

THE SICKLE-CELL TRAIT

A STUDY OF ITS DISTRIBUTION AND EFFECTS IN SOME BANTU
TRIBES OF SOUTH CENTRAL AFRICA

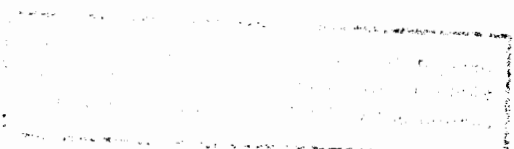
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THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF MEDICINE
UNIVERSITY OF CAPETOWN

1953



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TO MY FATHER

"We carry with us the wonders we seek without us; there is all Africa and her prodigies in us."

"New discoveries of the Earth discover new Diseases: for besides the common swarm, there are endemial and local Infirmities proper unto certain Regions, which in the whole Earth make no small number; and if Asia, Africa and America should bring in their List, Pandora's Box would swell, and there must be a strange Pathology."

Sir Thomas Browne

P R E F A C E

The scope of this work needs some explanation. I first became interested in the sickle-cell anomaly in 1951, while employed as a medical officer to an asbestos mining group in Southern Rhodesia. Here I had for investigation a population of several thousand adult male Bantu, very mixed as to tribe, drawn from a wide area of south Central Africa. The scope of this investigation has been determined by the nature of the material, which is in some respects unusual. This will be fully described later, but the important point is that in this population sickle-cell anaemia, if it occurs at all, is very rare. The sickle-cell trait, on the other hand, is frequently seen, and in a fit adult population of this kind it appears to exist virtually unadulterated by cases of sickle-cell anaemia either active or latent. This makes the population a peculiarly advantageous one for a study of the trait in its pure form, and it is the trait, and not the anaemia, that is dealt with in this thesis. The anaemia is treated only incidentally, and I should make it clear at the beginning that I can express no

authoritative views on it.

Three problems have specially interested me and are the subject of this work.

When in 1951 I first began to examine mine workers for sickling of the red cells, my interest in the subject was chiefly anthropological. Several authors had published papers showing interesting tribal and geographical variations in the incidence of sickling in Africa, and many of the tribes available to me had never been investigated. Sickling, like the blood groups, is one of the few simple genetically determined characters that show marked geographical variations in their distribution. These variations are of the greatest interest, though there is little agreement about their significance. My intention at this stage was to conduct a survey of the incidence of sickling in the tribes available to me, and to discuss, as far as the amateur in Bantu studies can, the ethnological significance of the findings. The first part of the thesis deals with this investigation.

A second problem soon presented itself. Up to this time, following many authors on the subject, I had regarded the sickle-cell trait as an undesirable characteristic, rendering its possessors liable to

various inconvenient complications such as infarction of the spleen, sudden death, and an increased liability to disease. As my collection of sicklers grew in size, the clinical impression became very strong that the trait was not producing these effects in my population. The question of the clinical significance of the sickle-cell trait has always been a controversial one. Although several authors have expressed opinions--for example that the trait predisposes to disease, that it is a stigma of degeneration, and that it is wholly innocuous--there is very little statistically supported evidence for or against the trait as a cause of morbidity. What evidence there is is contradictory. I therefore tried to plan an investigation that would show statistically whether the sicklers in my population suffered any disadvantage in health. The results confirmed the clinical impression that the trait is not a cause of morbidity. They suggested further--though this is far from conclusive--that trait-bearers might in fact enjoy a small advantage in health over normal subjects.

This question of the clinical significance of the trait is of course of obvious medical importance, considering the enormous numbers of trait-bearers that must exist in Central Africa alone; but it also has

theoretical implications of the utmost interest in the field of human genetics. The third problem is as follows. Patients with sickle-cell anaemia, as distinct from the trait, frequently die young, and if they survive to reproductive age have a greatly reduced fertility. One would thus imagine that with the elimination of these subjects, the frequency of sickling in populations would decline from generation to generation until it died out altogether. This does not happen, and it is clear that some mechanism, the nature of which is unknown, is keeping up the gene frequency. For convenience I have referred to this part of the work as the section on population genetics, though in the wider sense this is really the subject of the whole thesis. I have tried by a study of the trait to throw some light on this very complicated question. I should make it clear here that this part of the work is largely conjectural. Hardly any work has been done on this subject, and my views must be regarded as very tentative. I make no apology for this incursion into theory. Very little is known of the mechanism of human evolution, and the importance of the sickle-cell anomaly in its study may well exceed its purely medical significance.

The principal findings of this work, very briefly summarised, are as follows. An examination of about 3000 bloods from members of a number of Central African tribes showed tribal variations in sickling incidence from 0.6% to 27%, as well as geographical variations; these are discussed and some explanation attempted. The findings bear out the view of Lehmann that the sickle-cell trait was introduced into Africa from the East within comparatively recent times. Further, a suggestive parallel is pointed out between the distribution of sickling in Africa and that of the shorthorn zebu variety of Indian cattle, which is known to have been introduced comparatively recently from the East. It is suggested that the sickling gene may have been introduced and spread in Africa by the human migrants from the East who brought with them the short-horn zebu breed of cattle. The sickle-cell trait is found to have no discoverable pathological effects in the population examined by me, and the findings suggest that it might in fact confer a positive survival value. It is shown that of the mechanisms that might act in keeping up the frequency of the gene, only such a positive advantage enjoyed by the trait-bearer will reasonably account for the facts; and the view is advanced

that in sickling we have an example of a balanced polymorphism, the loss of anaemic individuals being balanced by a positive advantage in health enjoyed by trait-bearers.

The plan of the work is as follows. A short general introduction deals briefly with some important work in branches of the subject not dealt with in this work, to give perspective to the parts to follow. The body of the thesis is in two parts. The first deals with tribal and geographical variations in the incidence of sickling in Africa. In an introduction the literature is reviewed. After this my own findings are set out, and a section of discussion follows. The second part deals with the clinical significance of the trait and its population genetics, and is subdivided in the same way. A chapter on further problems, a detailed summary, Appendix and references follow.

A C K N O W L E D G M E N T S

Much of this work has been done five hundred miles from a medical library, and I must acknowledge with gratitude a very large amount of help and pleasant co-operation which I have received from workers in several countries who have sent information and reprints

of published work. I owe special debts of gratitude to my wife for much hard work, and to Dr. J.F. Murray of the South African Institute for Medical Research and Dr. J.V. Neel of the University of Michigan for advice and encouragement. My best thanks are due to the following correspondents: Dr. A.C. Allison, Dr. E.A. Beet, Dr. O. Budtz-Olsen, Dr. R. Elsdon-Dew, Dr. H. Foy, Dr. M. Gelfand, Dr. S.B. Griffiths, Dr. H. Lehmann, Médecin-Commandant J. Linhard, Dr. H. Osburn, Médecin-Colonel L. Pales, Dr. R.R. Race, F.R.S., Dr. A.B. Raper, and Dr. J.M. Vandepitte. The Rev. Fr. P. Galvin, and Mr. Roger Summers of the National Museum, Bulawayo, have given valuable advice on Bantu studies. To the late Dr. A.J. Ireland, Principal Medical Officer, Rhodesian and General Asbestos Corporation, I am indebted for facilities for investigation and permission to publish this work. I would like here to pay tribute to the memory of Dr. Ireland and to the interest he took in this and other investigations. To his successor, Dr. N. Walker, I am indebted in the same way. I am grateful to the Editor of the South African Medical Journal for permission to reproduce the tables in the section dealing with the clinical effects of the trait.

Shabani, June 1953.

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C H A P T E R I

G E N E R A L I N T R O D U C T I O N

In 1910 Herrick published his paper entitled "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anaemia." He observed these abnormally shaped cells in the peripheral blood of an anaemic negro student from Chicago, and his account was the earliest undisputed description of the sickle-cell abnormality in man. Herrick however was not the first to describe sickle-cells. In 1840 George Gulliver, F.R.S., Assistant Surgeon to the Royal Regiment of Horse Guards, had described sickle-shaped cells which he observed in the blood of several species of deer in the London Zoo. He illustrated these corpuscles, which were undoubtedly sickle-cells. The occurrence of sickle-cell anaemia in deer has more recently been confirmed (O'Roke, 1936). Gulliver described abnormally shaped cells from a number of other wild animals, but probably not all of these were genuine examples of sickle-cells. His methods of collecting blood from the larger animals must have called for much intrepidity.

For some years the diagnosis of sickle-cell

disease depended on finding sickled cells in smears made in the ordinary way from the peripheral blood. It is only in severe cases of sickle-cell anaemia that such cells appear. In 1927 Hahn and Gillespie investigated the mechanism of sickling. Using a hanging drop of blood contained in a gas chamber and observed microscopically, they demonstrated that sickling of susceptible red cells took place when their haemoglobin was deprived of oxygen, for example by passing carbon dioxide through the chamber; when oxygen was readmitted the cells reverted to the normal shape. As soon as this was recognised, methods to reduce the haemoglobin were applied to the red cells of apparently normal individuals, and brought to light numbers of non-anaemic individuals who had no sickled cells in the circulating blood but whose red cells could be induced to sickle when the haemoglobin was reduced. It has been estimated (Margolies, 1951) that about 7% of all American negroes show this abnormality, the sickle-cell trait. The ratio of those developing sickle-cell anaemia to the total number showing sickling has been estimated, in America, at various levels between 1 : 1.4 and 1 : 40 (Neel, 1949). Neel has shown that the expected, and probably the true ratio in American

negroes is about 1 : 44.

The most widely used method of eliciting sickling has been to seal a drop of blood between a slide and coverslip with vaseline. Air is thus excluded and the oxygen-consuming activity of the white and immature red cells gradually reduces the haemoglobin. A more elegant technique has been introduced by Beck and Hertz (1935), in which a suspension of red cells in a tube is sealed with liquid paraffin; the principle is the same. Recently several more rapid methods have been suggested. The haemoglobin may be quickly reduced by adding to the blood a culture of oxygen-consuming organisms; faecal bacteria (Singer and Robin, 1948) and even trypanosomes (Murgatroyd, 1948) have been suggested for this purpose. It is simpler still to add a solution of a chemical reducing agent such as sodium metabisulphite (Daland and Castle, 1948) which produces sickling in a few minutes.

Following the work of Hahn and Gillespie it became clear that the sickle-cell abnormality occurred in two more or less distinct varieties. Firstly there was the typical case of sickle-cell anaemia, which is a severe and incurable haemolytic disorder. Secondly, and much more commonly, the more or less

symptomless sickler occurred; these subjects did not develop sickle-cell anaemia and showed no very obvious ill effects of the sickling abnormality. This non-anaemic variety of sickling is known as the sickle-cell trait, or by the inelegant term "sicklaemia."

There are a number of differences between the anaemic condition and the trait. In sickle-cell anaemia, as we have seen, sickled cells may circulate in the peripheral blood; under physiological conditions of oxygen tension this does not occur in trait-bearers. The reason for this appears to be that in sickle-cell anaemia the red cells sickle at a less reduced oxygen tension than in the trait (Sherman, 1940). Transfusion experiments have shown that cells from patients with sickle-cell anaemia transfused into normal individuals have a much reduced survival time in the circulation, whereas the life of cells from trait-bearers similarly transfused is normal. (Singer et al., 1948, Callender and Nickel 1947). Sickle-cells of both the anaemia and the trait variety have a somewhat increased resistance to haemolytic agents by comparison with normal cells. The appearance of the sickled cells is different in the trait and in the anaemia (Foy, Kondi and Brass, 1951). In sickle-cell anaemia, blood sealed

under a coverslip begins to sickle at once and the red cells go on to develop long filamentous processes.

In the sickle-cell trait the onset of sickling is delayed and the long processes do not appear.

For some time it was not clearly recognised that there is an essential difference between the trait and the anaemia, and in particular it was not agreed whether carriers of the trait were liable to develop sickle-cell anaemia. The difference between the two conditions was further elucidated in 1949 by Pauling, Itano, Singer and Wells. By an electrophoretic method they showed that in sickling subjects an abnormal haemoglobin is present in the red cells. In sickle-cell anaemia the haemoglobin is all or predominantly of the abnormal variety; in the trait abnormal and normal haemoglobin coexist in the ratio of about two parts to three, though there is some variation in these proportions between individuals. Normal and sickle-cell haemoglobin have different electrophoretic mobilities, the sickle-cell variety moving as a more positive ion than the normal.

The mechanism of sickling appears to depend on the fact that the abnormal sickle-cell haemoglobin is

very insoluble when in the reduced state, though normally so when oxidised. At reduced oxygen tensions--which have to be lower in the trait than in the anaemia since less of the abnormal haemoglobin is present--the abnormal haemoglobin goes out of solution, forming elongated bodies known as tactoids and leading to the collapse of the cell envelope. When the haemoglobin is re-oxygenated the cell returns to its normal shape. The crystal structure of the abnormal haemoglobin has been investigated by Perutz, Liquori and Eirich (1951). They came to the somewhat unexpected conclusion that no difference in structure from normal haemoglobin could be revealed by X-rays, which suggests that the molecular structure of normal and sickle-cell haemoglobin must be extremely similar.

GENETICS OF SICKLING

For any study of sickling it is essential to understand its genetics. Although this work does not deal with sickle-cell anaemia, its place in the genetic system must be described.

It had early been observed that sickling had a familial incidence. Taliaferro and Huck (1923) from a study of a single large Negro family, showed that sickling is transmitted as a Mendelian dominant character.

This has been abundantly confirmed. It was assumed that the gene was variable in its expression and when strongly expressed gave rise to sickle-cell anaemia; when less strongly, to the trait. This theory would allow for all gradations between the trait and the anaemia. In 1949 Neel in America, and independently Beut in Northern Rhodesia, advanced the view that sickle-cell anaemia is a disease of individuals homozygous for the sickling gene. This means that for sickle-cell anaemia to develop, the individual must have a pair of the abnormal dominant genes giving rise to sickling; if he has only one abnormal gene (heterozygous state) he will show the trait but will not develop the anaemia. This is an exact parallel with the genetic situation in Mediterranean anaemia, which exists in the form of thalassaemia minor, corresponding with the sickle-cell trait, and thalassaemia major corresponding with sickle-cell anaemia. (Valentine and Neel, 1944). There seems little doubt that the very great majority of cases of sickle-cell anaemia do occur in those homozygous for the sickling gene; but what proportion of all homozygotes develop sickle-cell anaemia is a controversial question. Several workers, and especially Lehmann (1951) have criticised Neel's theory on

the grounds that not all homozygous sicklers develop sickle-cell anaemia. This question is further dealt with later.

By the theory of Neel and Beut, in its simple form, a subject with sickle-cell anaemia must have both parents positive for sickling, since he must obtain one of his pair of sickling genes from each parent; as the gene is dominant it cannot exist in the parent without giving rise to sickling. There are exceptions to this rule. Occasionally a case of sickle-cell anaemia is found having one parent negative for sickling; some of these are probably due to faulty technique, but one said by the authors to be reliable has been described by Foy, Kondi and Alexandrides (1951). Possible explanations in some of these cases may be that the legal and biological fathers are not the same; Foy et al. are convinced of the fidelity of the parents in their case, but in any event this explanation will not hold for two cases described by Singer (1951) in which the mother was the non-sickling parent. Here we may assume that the gene has arisen de novo in the mothers by mutation, but there is evidence that this must be an exceedingly rare occurrence. There are two other most interesting and more likely possibilities. Powell et al. (1950)

WORLD DISTRIBUTION OF SICKLING

This work deals with

the distribution of sickling in Africa, but a brief note on its occurrence elsewhere may be added. Sickling in the New World was introduced from Africa by the slave trade within comparatively recent historic times, and about 7% of American negroes show it. Outside Africa, the abnormality is found also in the Mediterranean basin, notably in Greece (Choremis et al., 1951). Caminopetros (1952) has made the somewhat alarming claim that 49% of the population of Athens show sickling; this, he hastens to add, is not a sign of Negro ancestry. Choremis (1952) and Lehmann (1952) have cast doubt on this finding. Dreyfuss and Benyesch (1951) had reported sickling in Yemenite Jews of Arabia, but this was not confirmed by Dreyfuss et al. (1952) who showed that sickling in this people could not be elicited by the use of chemical reducing agents. It seems possible that this may also be the explanation of Caminopetros' findings. There is no doubt, however, that some at least of the sickling discovered in the Mediterranean basin is genuine.

Recently Lehmann and Cutbush (1952 a and b) have reported the discovery of the sickle-cell trait in aboriginal tribes of south India. This very important discovery is dealt with later.

P A R T I

DISTRIBUTION OF SICKLING IN AFRICA

C H A P T E R I I

I N T R O D U C T I O N

Although the sickling abnormality had been known in America since 1910, in Africa very little work had been done on sickling up to the time of the second world war, and there was no information at all on variations in its geographical incidence. In the last ten years several studies of geographical incidence have appeared, and some investigators have further classified their subjects by tribe. There is still a great deal of work to be done in Africa before a detailed map of sickling distribution can be prepared.

The findings of investigators who have published results up to the end of 1952 are set out in the following Tables. Very fragmentary or doubtful results are not included, and where authors have subsequently published revised figures the earlier ones are not quoted. A uniform spelling of tribal names, not always the same as in the original papers, has been adopted.

Incidence of Sickling in West Africa

Region	Investigator	Remarks	Number examined	% sickling
West Africa	Evans (1944)	Soldiers Nigeria & Cameroons	362	13.3
		Gold Coast	136	16.6
		Gambia	67	23.3
		Total	561	19.9
West Africa	Findlay et al., (1948)	From Gold Coast, French Togo, Gambia, Sierra Leone, Nigeria	8500	12.4
Nigeria	Adamson (1961)	Males, Hausa tribe	200	17.5
Nigeria	Humphreys (1952)	Soldiers North	413	13.9
		East	138	19.5
		West	233	19.3
		Total	339	16.9
Western Nigeria	Jelliffe & Humphreys (1952)	Yoruba tribe	1331	23.7
Sierra Leone	Gooden & Reid (1943)	Hospital patients	1035	27
Gold Coast	Colbourne et al. (1950)	Villagers	201	22.4
Gold Coast	Edgington & Sarkies (1952)	At Accra	2251	13.1
French West Africa	Pales & Binnard (1952)	Guolof Iebou Bambara Toucouleur Foul	823 416 103 175 100	6.2 3.0 3.3 11.4 11.0
		Total, with other tribes	2302	3

Continued on next page.

T A B L E I

Incidence of Sickling in West Africa

Region	Investigator	Remarks	Number examined	% sickling
West Africa	Evans (1944)	Soldiers Nigeria & Cameroons Gold Coast Gambia Total	362 136 67 561	18.8 16.6 28.3 19.9
West Africa	Findlay et al., (1946)	From Gold Coast, French Togo, Gambia, Sierra Leone, Nigeria	5500	12.4
Nigeria	Adamson (1951)	Males, Hausa tribe	200	17.5
Nigeria	Humphreys (1952)	Soldiers North East West Total	418 138 283 839	13.9 19.5 19.8 16.9
Western Nigeria	Jelliffe & Humphreys (1952)	Yoruba tribe	1881	23.7
Sierra Leone	Gosden & Reid (1948)	Hospital patients	1035	27
Gold Coast	Colbourne et al. (1950)	Villagers	201	22.4
Gold Coast	Edington & Sarkies (1952)	At Accra	2251	18.1
French West Africa	Pales & Linhard (1952)	Ouolof Lebou Bambara Toucouleur Peul Total, with other tribes	623 416 108 175 109 2302	6.2 6.0 8.3 11.4 11.0 8

Continued on next page.

T A B L E I continued

Region	Investigator	Remarks	Number examined	% sickling
Portuguese Guinea,	de Azevedo & Coito (1948)		31	16
Portuguese Guinea, Bissau Is.	Trincão (1950)	Papel tribe	500	3
Cape Verde Is.	Nogueira et al., (1950)	Mostly half-castes	2500	3.04

T A B L E 2

Sickling in Portuguese East Africa

Portuguese East Africa	Tribe	Number	%
	Shonde	100	40
	Bakwa	110	39
	Loawe	100	4
	Osabe	100	3
	Tava	100	2
	Chapi	100	2
	Changam	150	2
	Ranga	100	1
	Tonga	100	1
	Nyoni		
	(? Salu)	50	1
	Don	50	1
	Tachana	50	2
	Manhaca	50	4

*It is not quite clear how a figure of 1% is obtained from a sample of 50.

T A B L E 2

Incidence of Sickling in Angola

Region	Investigator	Remarks	Number examined	% sickling
Angola	Teixeira (1944)		186	28
	Sarmento (1944)	Bantu	216	8.3
	Leite (1948)	Bantu	1973	7.24
	Trincao & Almeida (1948)	Bantu	36	8.3
		Pre-Bantu:		
		Bacuanodos	43	4.6
		Cuissis	70	10
		Curocas	27	3.7
		Mutuas	41	4.8

T A B L E 3

Incidence of Sickling in Portuguese East Africa

Portuguese East Africa	Foy et al., (1952)	Tribes:		
		Makonde	100	40
		Makua	110	38
		Lomwe	100	4
		Cuabo	100	3
		Tswa	100	2
		Chopi	100	2
		Shangaan	150	2
		Ronga	100	1
		Tonga	100	1
		Ngoni		
		(? Zulu)	50	1 ^x
		Sena	50	1 ^x
		Tachana	50	2
		Manhaua	50	4

^xIt is not made clear how a figure of 1% is obtained from a sample of 50.

T A B L E 4

Incidence of Sickling in Belgian Congo

Region	Investigator	Remarks	Number examined	% sickling
Katanga	Parent(1950)		1004	30.7
Whole territory	Vandepitte (1952a)	Soldiers	510	25.5
Belgian Congo	Lambotte-Legrand(1951)	Scholars	303	23.1
		Infants	392	24.0
	Van den Berghe & Janssen (1950)	Efe pygmies	456	25.9
		Bantu:		
		Luba	1020	20.0
		Mamvu	217	22.1
		Katanga	78	15.4
		Bakumu & Barumbi	552	5.6
		Bahutu & Batusi	1000	2.5
Ruanda-Urundi	Hiernaux (1952)	Batusi	294	1.3
		Bahutu:		
		Of Ruanda (with Tusi influence)		
			403	5.2
		Of Urundi	395	11.8
		Batwa pygmies	141	2.8
		Babinga " "	537	6.8
		Bashi (Bantu)	375	4.2

T A B L E 5

Incidence of Sickling in Northern Rhodesia

Region	Investigator	Remarks	Number examined	% sickling
Copper-belt	English (1945)	Adult male miners from several territories	717	17.5
Balovale district	Beet (1946)	Luvala tribe: N. Rhodesia Portuguese W. Africa	86	3.5
		Total, all tribes from district	815	12.9
Fort Jameson district	Beet (1947)	Chewa Angoni Senga Tumbuka	522 359 169 50	12.5 9.2 18.9 12.0
		Total, all tribes from district	1289	11.9
	Beet (1949)	Lunda Lala (children 6-18 yrs)	220 308	15.5 13.6

T A B L E 6

Incidence of Sickling in Southern Rhodesia
and the Union of South Africa

Region	Investigator	Remarks	Number examined	% sickling
Southern Rhodesia	Gelfand (1947)	From S. Rhodesia and surrounding territories	500	8
Union of S. Africa	Murray (1945)	From all parts of	50	0
	Altmann (1945)	Union of S.A.	403	0.25
	Griffiths (1951)	Cape Town: Cape Coloured adults	600	0.33
	Esrachowitz et al. (1952)		1555	0.58
South-West Africa	Griffiths (1953)	Bushmen: Barakwenga from Caprivi Strip	58	0
		From W. border of Bechuana-land	60	0
		Mpukushu tribe, from W. Caprivi Strip	119	0

T A B L E 7

Incidence of Sickling in Sudan and East Africa

Region	Investigator	Remarks	Number examined	% sickling
South Sudan	Abbott (1950)	Zande tribe	100	18
Tanganyika	Mackey (1949)	At Dar es Salaam:		
		Babies (1-18 months)	433	16.4
		Boys 12-18yrs	320	20.0
		Mothers	283	23.3
Uganda & Tanganyika	Lehmann & Milne (1949)	Secondary schools:		
		Mpwapwa, Tang.	125	38.4
		Mwiri, Uganda	240	29.2
		Makerere, Uganda	82	14.6
		Makerere College students	67	31.4
Uganda	Trowell & Muwazi (1945)	At Kampala; children with kwashiorkor	126	20
Uganda	Lehmann & Raper (1949)	HAMITES		
		Bahima	166	2.4
		Sebei	124	0.8
		Suk	128	3.9
		Karamojong	156	3.2
		Teso	416	17.8
		NILOTES		
		Lango	278	27
		Acholi	141	27
		Jaluo	130	28
		Lugbara	120	21
		Kakwa	101	25
		Alur	114	25
		Jonam	109	26
		Madi	109	3

Continued on next page

T A B L E 7

continued

Region	Investigator	Remarks	Number examined	% sickling
Uganda	Lehmann & Raper (continued)	BANTU		
		Bairu	139	2
		Banyaruanda	496	8
		Banyoro	91	12
		Batoro	120	12.5
		Baganda	740	19
		Bakonjo	102	18
		Barundi	108	19
		Bakenyi	88	26
		Basoga	241	29
		Bagishu	207	30
		Baamba	140	45

Several authors have attempted interpretations of their results from the ethnological point of view. The most extensive investigation thus interpreted is that of Lehmann and Raper (1949). They showed that in Uganda the Hamitic tribes have a uniformly low incidence of sickling (0.8 to 3.9%) with the exception of the Teso, who have been classed with the Hamites on linguistic grounds. Lehmann and Raper point out that the Teso lack the Caucasian features of the Hamites, and that they should probably be separated from them. The Nilotic group of Negro-Hamitic tribes along the upper reaches of the Nile are with the exception of the Madi very uniform in their incidence (21 to 27%). The Bantu, however, who consist also in the main of Negro-Hamitic mixtures but whose real unity is a linguistic one, show very marked variations in sickling incidence. Lehmann and Raper found 2% of sickling in the Bairu and 45% in the pygmoid Baamba. They showed that in the Bantu of Uganda the rate of sickling appeared to be inversely proportional to the extent of contact with the most recent Hamitic invaders. (Uganda lies in the northern limit of the territory occupied by the Bantu, in close proximity to Hamitic tribes.) The Bairu, for example, with a

sickling incidence of 2%, have lived for centuries as helots to the Hamitic Bahima. The Baamba on the other hand are a geographically secluded tribe, and of the tribes investigated they were furthest removed from the Bahima in appearance. The findings of Lehmann and Raper have been further elaborated by Wright (1951) from the viewpoint of the tribal historian.

In the Belgian Congo the same effect of Hamitic strains has been found by van den Berghe and Janssen (1950): the lowest incidence of sickling observed by them was 2.5% in the Bahutu, who had sustained mixture with Hamitic Batusi. The highest (26%) was again observed in a pygmoid race, the Efe pygmies. Hiernaux (1952) has shown however that not all pygmy tribes have a high incidence of sickling. The "yellow" pygmies of Central Africa have a low rate of sickling (Lehmann, 1953).

Elsdon-Dew (1950) commenting on the findings of Lehmann and Raper, observed that if the gene frequencies were calculated and the tribes arranged accordingly along a linear scale, the degrees of tribal mixtures could be estimated by the distance along such a line at which any particular tribe lay. The method will be used later in this work. Elsewhere Elsdon-Dew

(1951) has further considered the anthropological significance of the sickling gene. This work was based on Raper's view that sickle-cell anaemia does not occur in native Africans without a component derived from non-African stocks.

Beet (1946) offered an historical explanation of certain differences observed in the incidence of sickling in the Balovale district of Northern Rhodesia. He showed that in this district the Luvale living to the west of the Zambesi River showed an incidence of 3.5%, whereas those to the east of the river had an incidence of 16.7% similar to that in the Lunda (15.5%). He held that the distribution of sickling bore out the historical view that there had been considerable emigration across the river from west to east (i.e. from low-incidence Luvale to high-incidence Lunda) but little in the opposite direction. In his later paper (1947) from the Fort Jameson district, Beet again classified his subjects by tribe.

Foy et al. (1952) in Portuguese East Africa found in the north of the territory two tribes, the Makonde and Makua, having rates of sickling of about 40%; nowhere else in the territory was an incidence

of more than 4% observed. They remarked that these two northern tribes have pygmoid characteristics-- short stature, brachycephaly, and steatopygy--and that the Makonde speak an archaic variety of Bantu language. They suggested that they might represent the first wave of Bantu migration, unmixed with Hamitic blood.

Fales and Linhard (1952) showed that in French West Africa the lowest incidence observed was in the pure Sudanese negroes (6 to 8%) and that the highest was in the Guinea natives (16%).

The then known distribution of sickling in Africa was reviewed in 1952 by an annotator in the South African Medical Journal (1952, 26, 237) with a map. The author suggested that the trait probably arose in the region of the Ruwenzori mountains (giving rise to the mysterious name of "Mountains of the Moon") and that the rate of sickling becomes less the further from this region one goes in any direction.

Until quite recently it had always been assumed that the sickle-cell trait arose in Africa, since the only other regions in which it had been observed were either those populated comparatively recently by African emigrants (America and the West Indies) or the Mediterranean countries which have sustained some

African penetration since classical times. All the populations showing sickling possessed also a raised incidence of the distinctively African Rh chromosome cDe (Rh₀). (Mourant, 1951). This chromosome occurs in about 60% of Africans south of the Sahara (Mourant, 1951) and is very evenly distributed. In northern European countries and North India it has a frequency of about 2%. Another haematological peculiarity of the African is the rather rare He antigen (Ikin and Mourant 1951, Lehmann and Cutbush 1952a) which occurs in about 5% of West African negroes but not, as far as has been determined, in Europeans.

Because of this till then apparently exclusive connection of the sickling gene with Africa, the discovery by Lehmann and Cutbush (1952 a, b) of the trait in some aboriginal tribes of south India was an event of the first importance. Lehmann and Cutbush investigated the Veddids tribes in the region of the Nilgiri Hills. They represent the oldest and most primitive inhabitants of India and are found also in Ceylon. 201 Veddids showed an incidence of sickling of 31%. The cDe chromosome was not found in any of 156 Veddids tested, though 14 of them possessed the chromosome CDE (Rh₂) suggesting a link with Australasia. Two tribes

adjacent to the Veddids, the Badagas and Kotas, had sickling rates of 3.4% and 4% respectively. In other Indian peoples no sickle-cells were found. The He antigen was not found in India.

The Veddids of India thus show a high incidence of sickling with a low incidence of the negroid Rh chromosome cDe. This, as Lehmann and Cutbush point out, makes it unlikely that they received the sickling gene from Africa, since if this were so a raised incidence of cDe would be expected. A migration in the opposite direction--bringing the sickling gene to Africa from the East--they regard as more likely. An annotator in the British Medical Journal (1952, ii, 433) and Lehmann (1953) point out that in addition to South India and Ceylon, Veddids have been discovered in Persia and the Hadramaut, a region of southern Arabia from which there was formerly a land bridge to Africa in the vicinity of Aden. Lehmann suggests that the sickling gene entered Africa from the north-east comparatively recently, after the negro population had established itself. This would account for the observed distribution in Africa, which is still very patchy. By this view the sickle-cell trait is not a

genuine negroid characteristic but a character superimposed on the negro comparatively recently. The annotator previously mentioned makes the significant observation that the Malayan negritos tested by Polunin (1952) have a high cDe frequency but no sickle-cells. It has long been thought that there is some connection between the negritos of south Asia and those of Africa. Lehmann and Cutbush adduce other evidence in favour of a comparatively recent migration from the East to Africa. They observe that East African cattle and poultry resemble those of India, and that there are legends in East Africa of tall relatively fair long-haired men who came from afar bringing various amenities of civilisation with them.

DISTRIBUTION OF SICKLING IN AFRICA

CHAPTER III
ORIGINAL WORK

The work described in this chapter was carried out at Shabani and Mashaba, Southern Rhodesia, between 1951 and 1953. The same material was used for the whole investigation described in this thesis.

MATERIAL The investigation has been confined to adult male Bantu employed on the asbestos mines. There are several reasons for this choice, of which availability is the most obvious. The most important reason, however, is that the adult male population of mine workers contains very few closely related persons. As Elsdon-Dew (1950) has pointed out, it is of the utmost importance to avoid family groups if a true estimate of the incidence of a hereditary character is to be obtained. Furthermore, some authors have described variations in sickling incidence with age and sex. Where comparisons between tribal groups are to be made it is obviously of advantage to examine only one sex and age group.

There is another respect in which the population

examined is remarkable and perhaps unique. Although it includes many subjects from tribes with a high incidence of sickling, it must contain extremely few homozygous individuals, who are liable to sickle-cell anaemia. No case of sickle-cell anaemia, or of the sickling crisis, has been seen in this hospital in thirty years. The records are reliable since every mine worker who dies is taken to a complete autopsy and in doubtful cases histological examinations are made. The reason for this lack of homozygotes is apparently as follows. The local inhabitants of the Shabani and Mashaba districts, the Karanga, have an incidence of sickling of 0.6%, which should produce homozygotes at the rate of about one in thirty thousand births. It is thus not surprising that sickle-cell anaemia has not been observed in a local native. The sicklers in the mining population are almost all immigrants from north of the Zambesi River, where the incidence of sickling is higher; they do not usually bring their wives with them, but acquire local ones on arrival. Foy, Kondi and Brass (1951) have shown that at any rate in some parts of Africa most homozygous individuals die in infancy; those that survive are unlikely to be healthy enough to travel hundreds of

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miles to seek strenuous work. Probably all the sicklers found in the mining population are thus bearers of the trait alone and not candidates for the anaemia. Matings between these immigrant sicklers and local women also seldom produce homozygous sicklers, since these must have both parents positive for sickling and the local women have a very low incidence. For these reasons homozygous sicklers of any tribe are extremely rare in Southern Rhodesia, at any rate in the southern part where this work was done.

To confirm the belief that most if not all of the sicklers are trait-bearers and not homozygous sicklers without marked clinical manifestations, the haemoglobin levels of thirty unselected sicklers were measured and compared with those of thirty normal mine workers admitted to hospital with minor injuries. All determinations were made personally on the same instrument. Neel (1951b) has shown that in trait-bearers the haemoglobin levels are the same as in normal individuals, whereas in homozygous sicklers they are considerably lower. Table 8 shows that there is no difference between the groups; the means in fact are identical in the two groups. This lack of homozygous sicklers in the mining population is extremely important,

because it provides admirable material for a study of the effects of the trait uncomplicated by the presence of homozygous sicklers.

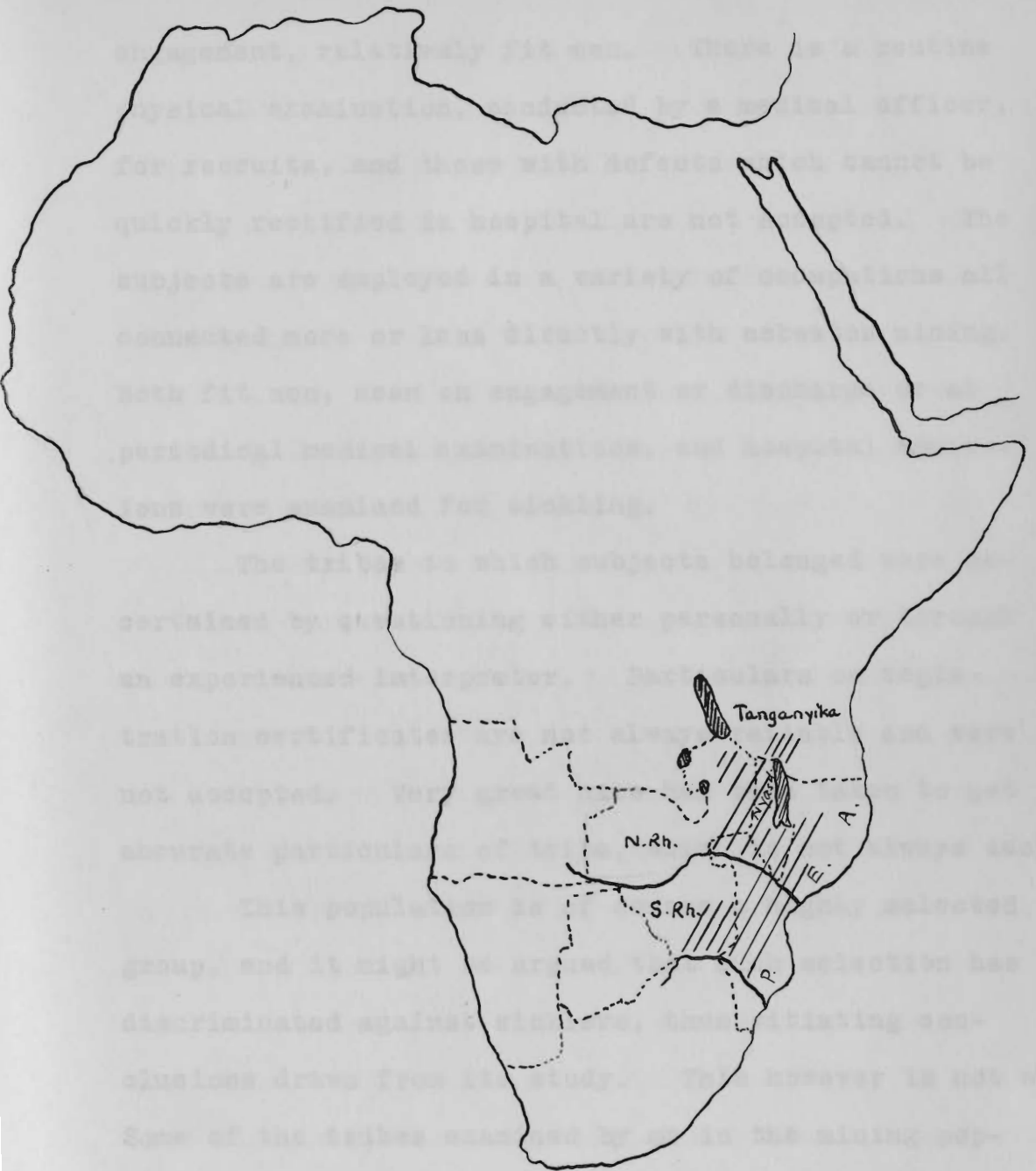
TABLE 3^x

Haemoglobin levels in Sicklers and Non-Sicklers

	Number examined	Haemoglobin, % (100% = 14.5 gm %)		Standard deviation, %
		Range	Mean	
SICKLERS	30	92-131	109	10.9
Non- Sicklers	30	87-140	109	10.7

The age limits in the population examined are not wide, though in the unsophisticated native age can only be estimated. None of the subjects is under about 17 years of age, and the majority are young adults. Very few are past middle age. The subjects are drawn from a wide area of south Central Africa, shown shaded on the map (Fig. 1); it includes parts of the two Rhodesias, Portuguese East Africa, Nyasaland and Tanganyika. All the subjects are, or were on

^x Table 3 and Tables 15 and 16 are reproduced by courtesy of the Editor of the South African Medical Journal.



F I G. 1

Parts of South Central Africa (shaded) from which subjects of the investigation are drawn.

engagement, relatively fit men. There is a routine physical examination, conducted by a medical officer, for recruits, and those with defects which cannot be quickly rectified in hospital are not accepted. The subjects are employed in a variety of occupations all connected more or less directly with asbestos mining. Both fit men, seen on engagement or discharge or at periodical medical examinations, and hospital admissions were examined for sickling.

The tribes to which subjects belonged were ascertained by questioning either personally or through an experienced interpreter. Particulars on registration certificates are not always reliable and were not accepted. Very great care has been taken to get accurate particulars of tribe, which is not always easy.

This population is of course a highly selected group, and it might be argued that such selection has discriminated against sicklers, thus vitiating conclusions drawn from its study. This however is not so. Some of the tribes examined by me in the mining population were investigated by other workers, notably Beet (1947) and Foy (1952) in their home surroundings. Of Beet's Northern Rhodesian tribes, only the Senga are strictly comparable with mine, since the Angoni and

Chewa in my population were drawn chiefly from Nyasaland, and Beet's chiefly from Northern Rhodesia where the incidence of sickling is higher. The differences between our findings for the Angoni and Chewa are nevertheless not statistically significant (Brain, 1952b). The Senga show the following rates of sickling: Beet 18.9% of 169 examinations, Brain 22.0% of 32 examinations. Thus my results show a higher (though not significantly so) percentage of sickling than Beet's. The results of Foy et al. (1952) are more difficult to compare, since many of their tribes were examined in widely separated places. For example their "Shangaans" extend from the Transvaal and Lourenco Marques up to Beira. Persons describing themselves as Shangaans in the vicinity of Beira are in all probability Shona-speaking Ndau, who will almost always appropriate the term "Shangaan"; results which follow show that there is a significant difference in sickling incidence between true Shangaans (Thonga-speaking) and Ndau. Similarly Angoni at Lourenco Marques are in all probability Zulu (Nguni) whereas those at Tete are probably from Gomani's Angoni of southern Nyasaland. An overall comparison is thus all that is possible. My population contained

none of the high-incidence Makonde and Makua; if the rest of Foy's findings after the exclusion of these tribes are compared with mine we find 1000 examinations by Foy et al. yielding 2.1% of sicklers, and 734 by me with 3.6%. The comparison of my results with those of these workers thus suggests that the incidence of sickling in my population is not lower than in theirs.

TECHNIQUE

Several techniques for eliciting sickling were tried, but only two have been used in obtaining the results quoted here: the tube method of Beck and Hertz (1935) and the metabisulphite method of Daland and Castle (1948). The commonly used method of sealing a drop of blood under a coverslip with vaseline, with or without preliminary constriction of the finger, and examining at intervals up to 48 hours was tried but soon abandoned. Among its disadvantages are the following: 1. Formation of rouleaux is troublesome unless the blood is mixed with saline before sealing. 2. Crenation of the red cells is often observed and may mask early forms of sickling. 3. Cells from known sicklers sometimes fail to sickle when tested by this method. This has been observed also by Jelliffe (1952).

For these reasons the sealed coverslip method was not used in the investigation at all.

The first thousand bloods were examined by a slightly modified Beck and Hertz tube method. A drop of capillary blood was collected in 1 cc of a 3.3% aqueous solution of sodium citrate in a flat-bottomed glass tube, and the suspension covered with a layer of liquid paraffin about 1 cm. thick, taking care not to entrap air bubbles. The tubes were kept for 24 hours at room temperature, which was that of a tropical summer. At the end of this time 1 cc of formol-saline (1 part of 40% formaldehyde solution to 3 parts of normal saline) was injected under the surface of the paraffin, still introducing no air, the the corpuscles re-suspended by stirring. After five minutes a drop of the suspension was pipetted off and examined with the microscope.

This is an admirable but time-consuming method. Tested on known sicklers it repeatedly gave consistent results and there was never any doubt whether a preparation was positive.

After the first thousand bloods had been examined it was suggested by Dr. J.F. Murray that one of the newer rapid methods might be tried. From the variety of reducing agents available, sodium

metabisulphite ($\text{Na}_2\text{S}_2\text{O}_5$) was chosen; this is recommended by Daland and Castle as being the most potent of the agents which they tested. The technique is as follows. A drop of capillary blood is taken on a slide and a drop of 2% aqueous solution of the metabisulphite added. A coverslip is applied but not sealed. Sickling is extremely rapid and is complete in five minutes or less. The only difficulty encountered with this method is that sickling may be further advanced in some parts of the preparation--not necessarily the centre--than in others, and it is necessary to examine several microscopic fields before pronouncing a preparation negative. This method revealed the same proportion of sicklers in the second thousand bloods as the Beck and Hertz method did in the first, and appears to be very reliable; it certainly gives more consistent results than the sealed coverslip method, and known sicklers tested from day to day repeatedly gave positive results. The solution was made up freshly every day; even in hot weather it preserves its sickling power for a week or more, but with solutions more than a day old the red cells tend to break up more rapidly and doubtful forms may appear near the edges of the coverslip.

Jelliffe (1952) in Nigeria regards the rapid chemical methods as unreliable in the tropics, since "the chemicals used are unstable and have to be freshly prepared at frequent intervals"; he therefore uses the sealed coverslip method. This is not my experience, though Nigeria is perhaps a hotter part of Africa. Over 2000 examinations were made in Southern Rhodesia using one sample of sodium metabisulphite (B.D.H. reagent) from which solutions were prepared as required. After nearly two years the reagent had lost none of its sickling power. It is very little trouble to make up 10cc of solution for each day's examinations.

With both the tube and the metabisulphite methods sickling may go no further than the so-called "holly-wreath" stage, though elongated cells were often seen particularly with the metabisulphite technique. The early holly-wreath stage is very distinctive and with experience it is unmistakable.

Sodium hyposulphite $\text{Na}_2\text{S}_2\text{O}_4$, as recommended by Williams and Mackey (1949) was also tried, but in rate of sickling was found to be very inferior to the metabisulphite. Potassium metabisulphite $\text{K}_2\text{S}_2\text{O}_5$, commonly used in photography, appears to be as effective as the sodium salt.

R E S U L T S

GEOGRAPHICAL AND TRIBAL DISTRIBUTION OF SICKLING

In this part of the investigation 3081 bloods were examined, and 143 sicklers were found. Because of the heterogeneity of the population the overall percentage incidence of 4.3% has little meaning.

GEOGRAPHICAL INCIDENCE The numbers examined from each territory, and the proportions of sicklers, are shown in Table 9.

T A B L E 9

Geographical Distribution of Sickle-Cell Trait

Country	Number examined	Number sickling	% sickling
S. Rhodesia	1104	7	0.6
Portuguese E. Africa	734	23	3.6
N. Rhodesia	245	41	16.7
Nyasaland	804	50	6.2
Tanganyika	144	22	15.3

It is important to note that these are not overall figures for the whole of any territory. They show simply the proportions of sicklers in the material from each territory available to me. As Fig. 1 shows, none of the territories has been completely covered by the investigation. Southern Rhodesia is represented by its south-eastern part. Portuguese East Africa has been covered except for the extreme northern and southern ends. Northern Rhodesia is represented by some tribes along its eastern border. Southern and Central Nyasaland are well represented, the north less completely. Tanganyika has only a small area at the north end of Lake Nyasa. In any event overall estimates of incidence for areas the size of these territories are of little value, since every territory shows significant geographical and tribal variations in incidence within its borders. These finer differences are next considered.

TRIBAL DISTRIBUTION Only the 13 tribes from which adequate numbers have been examined are considered here. The locations of these tribes are shown on the map (Fig. 2)^x which also shows percentage incidences of sickling. Notes on the tribal groups will be found in

^x See back end papers.

the Appendix. The incidence of sickling in the various tribal groups is shown in Table 10, in which the tribes have also been geographically subdivided. For each group the frequency p of the sickling gene has been calculated by the method of Neel (1951a): Frequency of sickling in population = $2p(1 - p)$. This formula incorporates a correction for the fact that homozygous sicklers are seldom found in adult populations, and is thus preferable to the simpler method used by Elsdon-Dew (1950). In the Table the figures for the Bemba and Bisa tribes of Northern Rhodesia have been combined. This was done because the numbers available from these tribes were small, and the tribes are related and contiguous. Even when combined the numbers are not large, but it is plain that the group possesses a high incidence of sickling.

STATISTICAL ANALYSIS OF TRIBAL INCIDENCE

The significance of the observed differences is shown in Table 11, which is arranged on the system of Elsdon-Dew (1939). The figures in the table are the results of dividing each difference between observed tribal incidences by its standard error, and following the conventional standard a figure of 2 or more indicates

TABLE 10

Tribal Distribution of Sickling

TRIBE	Number examd.	Number sick- ling.	% sick- ling	Geographical subdivisions (Numbers sickling in brackets)					
				p	S.Rh.	P.E.A.	Nyas.	N.Rh.	Tang.
Angoni	226	14	6.2	.033	1(0)	21(1)	131(9)*	22(4)	1(0)
Anguru	101	0	0	0	-	60(0)	41(0)	-	-
Bemba-Bisa	37	10	27.0	.163	-	-	2(0)	34(9)	1(1)
Chewa	275	26	9.5	.050	-	4(0)	226(21) ^x	45(5)	-
Cikunda	54	7	13.0	.070	-	51(6)	3(1)	-	-
Karanga	956	6	0.63	.005	956(6)	-	-	-	-
Ndau	313	11	3.5	.013	10(0)	303(11)	-	-	-
Nyakyusa	103	20	13.5	.103	-	-	-	-	103(20)
Nyanja	113	4	3.4	.013	-	20(0)	98(4)	-	-
Sena	142	9	6.3	.033	-	134(8)	3(1)	-	-
Senga	82	13	22.0	.123	1(0)	7(1)	-	74(17)	-
Shangaan	136	0	0	0	7(0)	129(0)	-	-	-
Yao	139	6	3.2	.013	1(0)	26(0)	161(6)	-	1(0)

* Nyasaland Angoni 5.0%, $p = .025$. Nyasaland Chewa 9.3%, $p = .050$.

T A B L E 10

Tribal Distribution of Sickling

TRIBE	Number examd.	Number sick- ling.	%sick- ling	p	Geographical subdivisions (Numbers sickling in brackets)				
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Anguru	101	0	0	0	-	60(0)	41(0)	-	-
Bemba-Bisa	37	10	27.0	.163	-	-	2(0)	34(9)	1(1)
Chewa	275	26	9.5	.050	-	4(0)	226(21) ^x	45(5)	-
Cikunda	54	7	13.0	.070	-	51(6)	3(1)	-	-
Karanga	956	6	0.63	.005	956(6)	-	-	-	-
Ndau	318	11	3.5	.018	10(0)	308(11)	-	-	-
Nyakyusa	108	20	18.5	.103	-	-	-	-	108(20)
Nyanja	118	4	3.4	.018	-	20(0)	98(4)	-	-
Sena	142	9	6.3	.033	-	134(8)	8(1)	-	-
Senga	82	18	22.0	.128	1(0)	7(1)	-	74(17)	-
Shangaan	136	0	0	0	7(0)	129(0)	-	-	-
Yao	189	6	3.2	.018	1(0)	26(0)	161(6)	-	1(0)

^x Nyasaland Angoni 5.0%, p = .025. Nyasaland Chewa 9.3%, p = .050.

a significant difference--that is, one which might be expected as a result of chance only five times in a hundred investigations.

As my own figures for the Northern Rhodesian Angoni and Chewa are inadequate, they have been combined for statistical purposes with those of Beet (1947) as follows (Numbers of sicklers in brackets):

Angoni: Beet 359 (33): Brain 22 (4): total 381 (37):
9.7%: $p = .050$.

Chewa: Beet 522 (65): Brain 45 (5): total 567 (70):
12.3%: $p = .0675$.

The Senga have been similarly combined, though this is not strictly essential:

Senga: Beet 169 (32): Brain 82 (18): total 251 (50):
20%: $p = .1125$.

These combined figures are used in the statistical analysis and on the map (Fig. 2), but not in Table 10, which contains only my own findings.

The significance of differences is shown graphically in Fig. 3, in which tribes whose names are enclosed in any one rectangle do not differ significantly among themselves in sickling incidence.

TABLE 11

Significance of Inter-Tribal Differences

	Angoni N. Rh.	Angoni N. Rh.	Anguru	Bemba-Bisa	Chewa N. Rh.	Chewa N. Rh.	Cikunda	Karanga	Ndau	Nyakyusa	Nyanja	Sena	Senga	Shangaan
Angoni N. Rh.	1.9													
Anguru	2.1	3.2												
Bemba-Bisa	4.3	3.3	9.3											
Chewa N. Rh.	1.7	0.2	3.3	3.0										
Chewa N. Rh.	2.9	1.4	3.8	2.6	1.2									
Cikunda	2.0	1.7	3.7	1.7	1.5	0.2								
Karanga	4.9	9.1	0.7	12.6	7.9	10.2	7.6							
Ndau	0.8	3.3	1.9	5.7	2.8	4.4	3.0	3.9						
Nyakyusa	3.9	2.5	4.4	1.1	2.4	1.8	0.9	11.5	5.4					
Nyanja	0.7	2.2	1.9	4.4	2.0	2.8	2.3	2.9	0.1	3.8				
Sena	0.6	1.2	2.5	3.6	1.0	2.1	1.6	5.3	1.4	2.9	1.1			
Senga	4.4	3.7	4.9	1.0	3.2	2.8	1.2	12.5	6.4	0.3	6.7	3.6		
Shangaan	2.7	3.9	0.0	6.1	3.6	4.2	4.2	1.0	2.2	5.3	2.2	3.1	5.6	
Yao	0.9	2.7	1.8	5.2	2.4	3.6	2.9	3.4	0.2	4.0	0.1	1.4	5.2	2.1

Note: The figures are the quotients Observed difference / standard error.

Significance of Inter-Tribal Differences

The rectangles enclose the names of tribes which do not differ significantly in incidence among themselves.

SHANGAAN	
KARANGA	
ANGURU	
YAO	
NYANJA	
NDAU	
ANGONI (Nyas.)	
SENA	
CHEWA (Nyas.)	
ANGONI (N.Rh.)	
CHEWA (N.Rh.)	
CIKUNDA	
NYAKYUSA	
SENGA	
BEMBA-BISA	

DISTRIBUTION OF SICKLING IN AFRICA

CHAPTER IV

DISCUSSION

All the available findings for Africa, including my own, have been used to prepare the map (Fig. 4)^x which shows the general distribution of sickling in the continent as far as it is known. In a map of this scale the fine differences in incidence revealed, for example, by the survey of Lehmann and Raper in Uganda cannot be represented; and for most other parts such detailed information is not available. Nevertheless the map gives an idea of the distribution of high and low incidence areas in Africa. My own results are further considered in more detail later, with a map on a larger scale.

Several facts are immediately obvious. The pure Negroes (non-Bantu) of West Africa show a more or less uniform incidence of sickling, averaging between 10 and 20%; no very remarkable tribal variations have been discovered among them. The Central African Bantu form a block of fairly high incidence (over 20% on the whole) extending probably right across the continent from about 5 deg. N to 15 deg. S. There may of course be uninvestigated variations within this block. In it

^x See front end-papers.

the general incidence appears to be rather higher towards the east, and all the known areas of over 30% incidence are nearer to the east than to the west. At the northern limits of this high-incidence block the incidence in the Bantu varies, as we have seen, with the extent of contact with recent Hamitic invaders; elsewhere it appears to be generally high.

In the Southern Bantu, whose northern boundary is usually delimited by the Zambesi and Kunene Rivers, the incidence of sickling is almost everywhere very low (less than 1% in the Union of South Africa and the Karanga of Southern Rhodesia.) There is no reliable estimate of incidence in the northern part of Southern Rhodesia, since the sample examined by Gelfand included immigrants from outside the Colony; but as these would be from northern territories of higher incidence (immigration from the south does not take place) it is probably safe to say that the incidence in the north of Southern Rhodesia must be below 8%. The low-incidence southern block appears to extend for some distance north of the Zambesi mouth on the east coast (incidences of less than 4% found by both Foy et al. (1952) and myself in this region): it ends abruptly to the north with the Makua tribe who have an incidence of 38% (Foy et al.).

The area covered by my own survey will now be considered in more detail.

The map (Fig. 2, see back end-papers) shows the regions covered by the survey, together with the names of tribes and percentage incidences of sickling. Findings of other investigators that have been added to the map are those for the Makonde and Makua of Foy et al. (1952) and the Tumbuka and Lala of Beet (1947, 1949). The Northern Rhodesian findings of Beet (1947) for the Senga, Chewa and Angoni have, as we have already seen, been combined with my own for the purposes of this map.

The map shows that the Karanga of Southern Rhodesia, of whom a large sample (956) has been investigated, show the low incidence of sickling (0.6%) that is typical of the Bantu of the Union of South Africa. From the ethnological point of view this is superficially an interesting finding. The Shona of Southern Rhodesia, of whom the Karanga form part, constitute in some respects an intermediate group between the Southern and Central Bantu (Junod, 1938). Like the southern tribes they are patrilineal and patrilocal (see Appendix); but in language and their development of totemism they are closer to the northern tribes such as the Nyanja

than they are to southern groups such as the Sotho and Zulu. The incidence of sickling in the Karanga would place them unequivocally in the Southern Bantu. We shall see later, however, that this argument is probably unjustified. The Ndau to the east and north-east of the Karanga, who are also a Shona group, show a significantly higher incidence of sickling than the Karanga; this is probably because they extend further to the north. The Ndau also show a significant difference from the Shangaans in the south; there is a very marked linguistic difference between the groups.

In the north of Southern Rhodesia, as we have seen, the incidence of sickling is probably rather less than 8%. As we reach the Zambesi River the incidence increases rapidly (13% in the Cikunda, 20% in the Senga) except in the east at the mouth of the river where it does not exceed 4%. We have already seen that the southern low-incidence block extends some distance north of the Zambesi on the east coast.

In the region of the southern end of Lake Nyasa there is an interesting gradient of increasing incidence from east to west. The Anguru and Yao have a low incidence which is shared by the Nyanja on the lake shore (3.4%). Further west the incidence increases

through the Chewa of Nyasaland (9%) and of Northern Rhodesia (12%) to the Senga^x (20%). The history of these tribes will be found in the Appendix; briefly, the Yao and Nyanja are closely related, and the Chewa and Senga are comparatively recent offshoots of the Nyanja who have spread westward in the past two centuries, approximating more and more in language to the Bemba-Bisa-Lala group with whom they have intermarried (Tew, 1950). This linguistic gradient from Nyanja to Bemba-Bisa-Lala is paralleled by an increasing incidence of sickling, from 3% in the Nyanja through 9 and 12% in the Chewa to 20% in the Senga and 27% in the Bemba-Bisa. In fact most of the intermarriage between the Senga and the western tribes has been with the Lenje (see map); they are related to the Lala but their incidence of sickling is not known. It could safely be predicted that it is higher than that in the Senga-- i.e. over 20%. If the incidence of 27% in the Bemba and Bisa is taken as an estimate for the whole western group of Bemba, Bisa, Lala and Lenje, we may apply the method of Elsdon-Dew (1950) to estimate the percentage

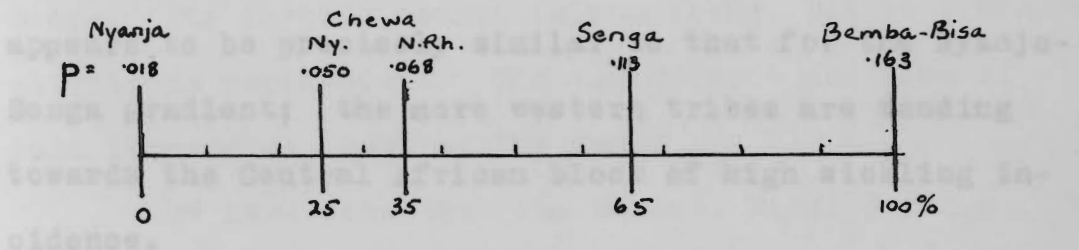
^x It is important to note that these Senga are the southern group of that name, and not the more northern Ansenga Chomeni who are of Bemba-Bisa stock and did not spring from the Nyanja.

composition of these groups, as follows:

If the Nyanja at a gene frequency of .018 are regarded as having no Bemba-Bisa admixture, and the Bemba-Bisa at .163 as having no Nyanja blood, the intermediate tribes can be arranged along a line of increasing gene frequency as follows, and distances along such a line can be used to calculate the percentage composition of the tribes:

FIG. 5

Estimated Percentage Composition of some Tribes



These figures are only approximations because (a) the incidence of sickling found in the Bemba-Bisa comes from a very small sample (b) there are probably variations in incidence between tribes of the Bemba-Bisa-Lala-Lenje group and (c) the Senga are probably tending towards the incidence in the Lenje whereas the more northern

Chewa are probably mixing with the Bemba and Bisa.

Nevertheless the figures give some idea of the composition of the tribes. They suggest that the Chewa have on the average about 70% of Nyanja and 30% of Bemba-Bisa in their genetic composition, and the Senga about 65% of Bemba-Bisa.

In the riverine peoples on the Zambesi banks the same effect is to be observed, though these peoples are less homogeneous. At the mouth of the river on the east coast the Cuabo show a low incidence (less than 4%). Rather further upstream the incidence increases through the Sena (6%) to the Cikunda (13%) who are related to the Senga. The reason for this appears to be precisely similar to that for the Nyanja-Senga gradient; the more western tribes are tending towards the Central African block of high sickling incidence.

The two groups of Angoni for which figures of sickling incidence are available are the Northern Rhodesian Angoni of Fort Jameson and the groups of Gomani and Ciwere in Southern Nyasaland. Both of these main groups are settled among the Chewa, and both show a rather lower incidence of sickling than the Chewa of the regions in which they have settled. This is what

would be expected on historical grounds (see Appendix), where relatively small contingents of invaders from the south, with a very low sickling incidence, have intermarried with more numerous local inhabitants having a higher rate of sickling.

From the map it is clear that the border of the Central African high-incidence block can be defined for some distance. A convenient limit is the isogene $p = 0.1$, corresponding to an adult incidence of 18%. This passes from the east coast along the southern border of the Makua, over the north end of Lake Nyasa, and then south-west along the eastern border of the Bemba-Bisa group to the Zambesi in the region of the Senga. Its further course is uncertain, but it probably turns north-west. The approximate position of this isogene is shewn on the map.

We have seen that the Zambesi River forms a boundary between low-incidence tribes to the south and those of higher incidence to the north. It also forms the boundary of the Southern Bantu, and is thus a cultural as well as a geographical barrier between patrilineal tribes to the south and those predominantly matrilineal to the north. As far as our knowledge goes--and it is by no means complete--the Bantu tribes

south of the Zambesi appear to have a generally and uniformly low incidence of sickling, although in the extreme north this is probably somewhat raised by contact with higher-incidence tribes along the river. Junod (1938) has suggested that the matrilineal system is the older, and that the Southern Bantu, though patrilineal, still show traces of the old matrilineal system. The uniformly low incidence of sickling south of the Zambesi might suggest that the whole group of Southern Bantu, in whom the patrilineal system of descent has been superimposed on an earlier matrilineal system, is a real ethnological unit. Blood-group findings in the Southern Bantu might be used to test this theory, but unfortunately this is a subject on which authorities disagree. Elsdon-Dew (1939) observed significant differences in the incidence of the ABO groups between tribes south of the Zambesi, as well as affinities with more northern tribes. For the Union of South Africa these findings were disputed by Shapiro (1951) who maintained that the South African Bantu were serologically a homogeneous group. The blood groups seem to be unique in the amount of scientific controversy to which they give rise, but it does seem probable that Shapiro's findings will have to be confirmed before

his criticisms of Elsdon-Dew's results can be accepted. We shall return later to the significance of the sickle-cell findings in this question.

ORIGIN OF THE SICKLE-CELL PHENOMENON IN AFRICA We

have already seen that Lehmann and Cutbush have observed the sickle-cell trait in aboriginal Veddid tribes of South India, and that other Veddid groups have been described in Persia and South Arabia. It has been suggested (Lehmann, 1953) that the sickling gene was in fact brought to Africa at a time when the negroes were already established, and that it entered Africa across the strait of Bab-el-Mandeb at the southern end of the Red Sea. There seems little doubt from the evidence of the Rh groups already mentioned that such a migration, if it occurred at all, was from east to west, bringing the gene from Asia to Africa, and not in the opposite direction. By the principle of economy of hypothesis we must connect the sicklers in India with those in Africa if the facts will allow it, and not assume independent mutations in the two places. From the patchiness of sickle-cell distribution in Africa, and in particular from the very low incidence of the gene south of the Zambesi River, it seems quite clear that the original nucleus of the Bantu did not possess

the gene--in contrast, for example, with the Rh chromosome cDe which they certainly possessed and which is now very uniformly distributed in black Africa. Junod (1938) estimates the age of the Bantu at between two and three thousand years, and suggests that they originated in the region of the Great Lakes as a group speaking the same language. Their linguistic unity is still their most remarkable, if not their only, common characteristic. The superimposition of the sickling gene on the already differentiated Bantu would thus account for the known incidence of sickling in the Bantu tribes. As the map (Fig. 4) shows, the areas of highest sickling incidence are still to be found in the region of the east coast of Tanganyika and in Uganda, where they would be expected if the gene had entered from the north-east. One would have to postulate that the sickling invasion spread in a southern and western direction but stopped at the Zambesi River, to account for the virtual absence of sickling in the Southern Bantu.

There is one apparent objection to this otherwise attractive theory. The true negroes of West Africa have been separated from the Bantu, who are basically a Negro-Hamitic mixture, for thousands of years, and

linguistically they are totally different from the Bantu. It is very unlikely that, if the Bantu received the sickling gene comparatively recently from the East and distributed it among themselves, the West Africans would show the moderately high and uniform incidence of sickling, averaging about 15%, that they do. The fact that both the West African Negroes and the Bantu possess the gene in fairly high proportions might suggest that it was a negroid characteristic before the Negro-Bantu differentiation took place. If this were so, one would expect the Bantu, who consist of Negroes diluted with Hamitic strains of known low incidence, to show a lower incidence than the pure negroes of West Africa. This has also been remarked by Foy, Kondi and Hargreaves (1952). In fact, the incidence in the Bantu is in many parts of Africa higher than it is anywhere in the negroes of West Africa. And as we have already seen, if the gene had been present in the original Bantu one would expect a more uniform distribution than one in fact finds in the Bantu tribes of today. The evidence that may resolve this apparent contradiction comes from an unexpected source, the migrations of cattle in Africa.

Dart (1951) in his work on the ABO blood groups

in Africa (African Serological Patterns and Human Migrations) has a chapter (p. 25) on the place of oxen in South African migrations. In this he quotes a paper by Bisschop (1937) on "Derived Types of African Cattle." Bisschop observes that cattle apparently originated in Asia; they came to Africa and Europe with early human migrations but did not exist in the New World or Australasia until taken there by Europeans. Three types of cattle are of particular interest to us:

1. The Hamitic or Egyptian long-horn (*Bos hamiticus*) was domesticated in Egypt in Neolithic times and spread westwards along the coast of North Africa to Gibraltar, and thence north to Spain and south to West Africa.

2. The Longhorn or Lateral-Horn Zebu (*Bos indicus*) the first humped cattle in Africa. These cattle were brought to Africa in about 2000 B.C. by Semitic tribes from North-West India, through Arabia into what is now Somaliland, and spread over Ethiopia and upper Egypt. Epstein (1933) has suggested that pure longhorn zebu cattle accompanied the progenitors of the Hottentots--who according to Elsdon-Dew (1939) are serologically similar to the Egyptians--on the first southward human migration that was accompanied

by cattle. The later Bantu migrations brought with them the Sanga cattle, a cross between the Hamitic and Zebu longhorns. Since the Bantu did not reach as far south as the Western Province of the Cape, the Hottentot cattle found by van Riebeeck was pure longhorn Zebu and have given rise to the Afrikander breed in South Africa today (Bisschop, 1937).

3. The Shorthorn Zebu, which Epstein thinks is a cross between the Longhorn Zebu and a shorthorned species *B. brachyceros*, but Bisschop regards as an independent subspecies of the longhorn zebu. It differs from the longhorn zebu principally in the horns and the hump. Dart quotes Bisschop, with his own additions in parentheses, as follows:

"The shorthorned Zebus arrived in Africa via Southern Arabia into Somaliland and Ethiopia within historic times, i.e. during the period when Persia (and also Vedic India and Himyaritic Arabia) was at the height of its power (i.e. 550 - 330 B.C.) and subsequently during the Arab penetration of North-Eastern Africa. Indians and Arabians are believed to be responsible for the shorthorned Zebu's migrations within this continent, especially down the East Coast to the Zambesi. Apparently, too, the shorthorned zebu

was carried across the continent to the Gulf of Guinea, since marked evidence exists there of its influence upon local cattle." The distribution of the short-horn zebu in Africa has been further considered by Curson and Thornton (1936).

Dart observes that the shorthorn zebu did not cross the Zambesi, although it was taken by sea to Madagascar. From the fact that it is not found south of the Zambesi he estimates that the shorthorn zebu invasion probably took place more recently than Bisschop thinks--probably after the Moslem settlement of Madagascar and the East Coast in about 700 A.D. Bisschop's route of migration of the shorthorn zebu is shown in Fig. 6, together with the approximate incidence of sickling.

I would suggest that the migration of the shorthorn zebu, taken in conjunction with the findings of Lehmann and Cutbush, offers some suggestive evidence:

(a) Lehmann and Cutbush, and Lehmann (1953) have suggested that the sickling gene was introduced into Africa from India via South Arabia within comparatively recent times, since the establishment of the black races. The shorthorn zebu was introduced by Indians and Arabians, via south Arabia, within historic

times.

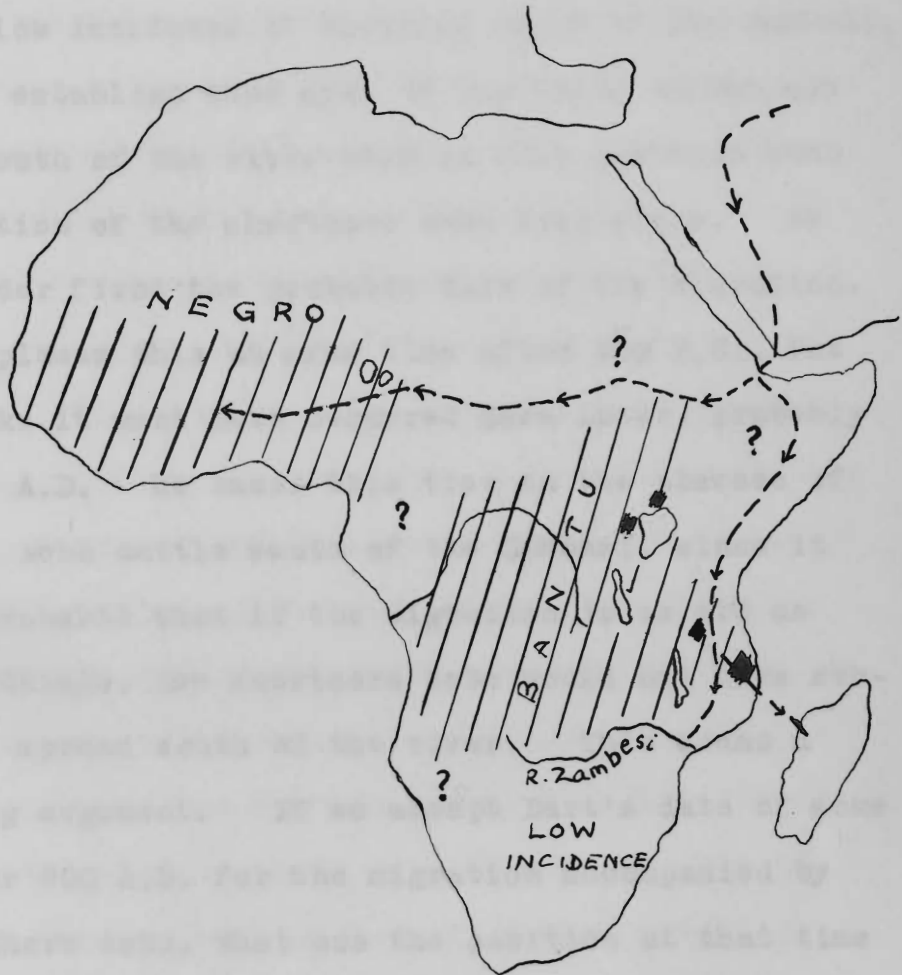
(b) Sickling is found in both the Bantu and the negroes of West Africa; so is the shorthorn zebu.

(c) Sickling is widely distributed in the Bantu of Central Africa, but is rare south of the Zambesi; the shorthorn zebu has exactly this distribution, and did not cross the Zambesi.

(d) The known areas of highest sickling incidence in Africa are all nearer to the east coast, near the point of introduction suggested by Lehmann and on the line of Bisschop's southern migration of the shorthorn zebu (See Fig. 6). It seems possible that the sickling gene was introduced into Africa and spread in the continent by peoples from the east who were accompanied on their migrations by the shorthorn zebu variety of cattle, from the present distribution of which the paths of the human migration may be traced. These people spread both among the West African negroes and the Bantu. The difficulty of explaining the diffusion of the gene from the Bantu to the already differentiated West African negroes is thus removed.

It might be objected that not all of the tribes possessing a high sickling incidence are cattle-keeping. This is so; but it does not necessarily follow that

FIG. 6



Map showing routes of migration of shorthorn zebu cattle (after Bisschop, 1937). The shaded areas represent parts in which a sickling incidence of 10% or more has been observed.

----- route of migration
? incidence of sickling unknown

intermarriage between members of these tribes and the custodians of the zebu must necessarily result in the conversion of the tribe to zebu-keeping.

It is clear that this theory will account for the very low incidence of sickling south of the Zambesi, if we can establish that most of the Bantu tribes now settled south of the river were in this position when the migration of the shorthorn zebu took place. We may consider first the probable date of the migration. Bisschop places this at some time after 400 B.C., but Dart thinks it must have occurred much later, probably after 700 A.D. He bases this view on the absence of shorthorn zebu cattle south of the Zambesi, since it seems improbable that if the migration is as old as Bisschop thinks, the shorthorn zebu would not have subsequently spread south of the river. This seems a convincing argument. If we accept Dart's date of some time after 700 A.D. for the migration accompanied by the shorthorn zebu, what was the position at that time of the tribes who now make up the Southern Bantu?

The Bantu are thought to have originated in the region of the Great Lakes from a mingling of Negro with Hamitic or Mediterranean peoples. Before the coming of the Bantu the whole length of the continent

on the eastern side was occupied by a brown race, in the north Hamitic or Mediterranean, the type of the ancient Egyptians, and further to the south by the related Bush-Hottentot race (Dart, 1937). With the advent of the Bantu from the north the Bush peoples were absorbed or destroyed and only scattered pockets of them remain in Central Africa today. The Bantu, however, did not extend to the southernmost limits of Africa, and the Bush and Hottentot peoples were found in possession by the early navigators at the Cape of Good Hope. The exact date of appearance of the Bantu south of the Zambesi is uncertain, but there is little doubt that they arrived in several southward waves. Dart (1937) mentions Arab geographers from the tenth century onwards who reported the presence of Bantu on the east coast as far south as Sofala. He observes: "After destroying the Sabaeen power, the Abyssinians were able to maintain their own independence and to arrest the north-easterly flow of Bantu; but their relaxed grip on the Sabaeen East Coast ports and the gold-producing South African belt left the Bush natives of that territory an easy prey to the southward-advancing Bantu from the end of the sixth century (i.e. A.D.) onwards. We shall probably not be far wrong if we place

the first great southern migration of the Bantu at about this period."

Some of the archaeological evidence of pottery suggests a rather earlier date for the first southward migration of Bantu--probably at some time before Christ for the Sotho-Tswana invasion of the Union of South Africa. By the same evidence the Karanga of Southern Rhodesia and the Tonga-Ila along the Zambesi probably moved into position early in the Christian era. Dart (1937) thinks that the Nguni peoples of the Union of South Africa are probably representative of a very early southward migration of Bantu because of the presence of clicks, a distinctively Bush and non-Bantu feature, in their languages. It thus does not appear at all improbable that some if not all of the tribes making up the present Southern Bantu were already settled south of the Zambesi by the eighth century A.D.

The idea of Indian migrations to Africa is not as odd as it seems at first sight. Dart (1937) quotes Ingrams (1931) to the effect that Hindus had trading settlements on the East African coast from the seventh century B.C., and were acquainted, to judge from the Sanskrit scriptures, with the Great Lakes and the source of the Nile. The longhorn and shorthorn zebu cattle

were introduced into Africa from India. Dart (1937) has considered the distribution in Bantu Africa of the typically Asiatic brachycephalic skull form (the Bantu are dolichocephalic). Brachycephaly occurs in Africa in scattered "nests", and Dart suggests that further study would show that these are distributed along ancient routes of Asiatic trade.

This theory of the introduction of sickling supports in every detail the view of Lehmann (1953), that the sickling gene was introduced into Africa from the vicinity of Aden within comparatively recent times, after the differentiation of the black races, by migrants from India. One minor difficulty with which it has to contend is the low incidence of sickling along the part of the east coast immediately to the north of the Zambesi mouth up to the border of the high-incidence Makua. One would expect, if the shorthorn zebu migration extended down the east coast to the Zambesi, that a high incidence of sickling would be found all the way down the coast. Of the tribes now inhabiting this region, however, the Yao at any rate are linguistically and culturally almost identical with the Nyanja, who have a tradition of emigration from the Luba district of the Congo within the last 500 years. It is very

probable that these later invaders have displaced the high-incidence population to the regions now occupied by the Makonde and Makua. It would probably be found that the ancestors of the Makonde and Makua tribes occupied the east coast at the time of the shorthorn zebu migration southwards. The Makonde at any rate are said by Foy et al. (1952) to speak an archaic variety of Bantu language and probably represent an early wave of invasion. Other minor irregularities in the observed incidence of sickling might be accounted for in the same way by recent movements of Bantu tribes.

This theory makes clear several points which would otherwise be very hard to explain. The Hottentots of South Africa are, in their ABO groups at any rate, serologically identical with the Efe pygmies of the Congo (Dart, 1951); yet the incidence of sickling is 26% in the Efe (van den Berghe and Janssen, 1950) and probably very low indeed in the Hottentots to judge from the findings of Esrachowitz et al. (1952) in the Cape Coloured people. If we recognise the sickle-cell trait as a character imposed on tribes to the north of the Zambesi comparatively recently, there is no difficulty in reconciling these findings. We have seen also that in the Southern Bantu as a whole the incidence

of sickling is uniformly very low. This does not mean that they constitute an ethnological unit; they may do so, but all that the sickle-cell findings mean is that the sickling gene established itself in the Bantu after the establishment of the Southern Bantu in their present situation, and that the migration which brought it did not spread into their territory to any great extent.

If the view of Dart (1951) is correct, that the shorthorn zebu migration though stopping at the Zambesi extended across the sea into Madagascar, it should be found that the population of Madagascar has a considerably higher incidence of sickling than that of the adjacent mainland if sickling and the shorthorn zebu migration are connected.

If this view of the origin of sickling in Africa is the right one, it is clear that the value of the sickle-cell trait in anthropology is not as great as it would be if the trait were a less recent characteristic of the black races of Africa. As Lehmann (1953) points out, the sickling gene is a recent acquisition in black Africa, and unlike the cDe chromosome cannot be used as a reliable index of African ancestry.

P A R T I I

EFFECTS AND POPULATION GENETICS OF THE SICKLE-CELL TRAIT

C H A P T E R V

I N T R O D U C T I O N

It has never been disputed that sickle-cell anaemia, a severe haemolytic disorder, has marked clinical effects. The question of the clinical significance of the sickle-cell trait, however--that is, of the sickling gene in the heterozygous state--has always been a controversial one. A few of the opinions that have been expressed on the subject are set out below:

"With increasing knowledge the general trend of opinion has been to assign to the sickle-cell trait less and less significance" (Diggs et al., 1933).

"Persons showing the sickle-cell trait should be considered as potential sufferers from sickle-cell disease.....the term sickle-cell anaemia should be replaced by sickle-cell disease since anaemia is only one of the many manifestations of sicklaemia and probably not one of the most important ones" (Beet, 1947).

"In association with the trait alone, neither

anaemia nor the above symptoms" (i.e. symptoms due to impaction of sickled cells in bloodvessels) "are produced" (Wintrobe, 1951).

"We cannot agree with Wintrobe when he considers the sickle-cell trait to be of little clinical significance.....Having the sickle-cell trait he (i.e. the subject) may become the victim of his constitutional biological inferiority and succumb under circumstances which are innocuous to average normal people" (Bauer and Fisher, 1943).

As Diggs et al. (1933) remark: "Although many opinions have been expressed as to the significance of the sickle-cell trait, there are few facts and figures." Eighteen years later the question was still undecided and we find Neel (1951a) writing that "further detailed studies of the exact medical significance of the sickle-cell trait would seem to be highly desirable." In the section on results which follows I have tried to supply some of the facts and figures which are needed. In the remainder of this section the literature on the effects of the trait is reviewed. It is important to note that before 1949 the distinction between the trait and the anaemia was not always clearly drawn, though some authors such as Steinberg (1930) and Diggs et al. (1933)

had early recognised the essential difference between the two states. Reports clearly dealing with sickle-cell anaemia, or with other pathological manifestations in markedly anaemic subjects, are not considered here.

The evidence for or against the clinical significance of the sickle-cell trait is of several kinds. It may be roughly classified as follows, and is dealt with in this order:

(a) Investigations of the incidence of sickling in selected populations--e.g. fit men, hospital patients, and various age groups. Such investigations give indirect information about the effects of the trait. Thus if a higher incidence of the trait is found in hospital patients than in normal subjects, it is logical to assume that the trait predisposes to morbidity. If the incidence in young subjects is higher than in older ones, it can be argued that bearers of the trait have a higher death rate than normal people. If the trait is a cause of morbidity, one would expect to find a lower incidence in populations selected for physical fitness--e.g. soldiers--than in the population as a whole.

(b) Evidence derived from a direct study of trait-bearers, for example their physical measurements

as compared with those of normal people; and a study of specific effects which have been attributed to the possession of the trait.

(a) Incidence of Sickling in Selected Populations.

Henderson and Thornell (1946) found that in American Negro air cadets, who had passed a searching physical examination and constituted a very fit group, the incidence of sickling was 7.4%, whereas the average incidence for the whole Negro population is 7.25% (Margolies, 1951). This suggests that the physical examination which the cadets had undergone did not discriminate against bearers of the sickle-cell trait. Although this is probably a valid deduction, the source of the population of cadets was not stated, and hence some small difference may have gone unnoticed. The incidence of sickling in the American negro is known to vary somewhat from place to place, being highest in the negroes of South Carolina (13.4% found by Switzer 1950).

A number of investigators have examined the incidence of sickling in patients admitted to hospital, and compared it with the rate in fit subjects from the same population. There is little agreement in the results.

Evans (1944), working in West Africa, found that the incidence of sickling in 302 fit soldiers was 15.5%, whereas in 259 soldiers in hospital with various acute and chronic diseases the incidence was 25%. This is a highly significant difference (about four times its standard error.) The highest incidence (28.3%) was found in a subgroup of patients admitted with respiratory diseases, but this does not differ significantly from the rate in hospital patients as a whole. Findlay et al. (1946), using very similar military material in West Africa were unable to confirm these results; they found very similar rates in fit men and in hospital admissions including a long series with pneumonia. In the United States Diggs et al. (1933) obtained similar results with schoolchildren; the rate in 662 normal children was 9.7% and in 450 hospital admissions 9.3%. English (1945) on the Copperbelt of Northern Rhodesia observed no difference between the rate of sickling in fit mine workers and hospital admissions. His actual results however were not stated.

The incidence of sickling in patients admitted to hospital with tuberculosis was investigated by Dolgopol and Stitt (1929). They found that 77

T A B L E 1 2

Variations in the Incidence of Sickling with Age; U.S.A.

Investigator	Age Group	No. examined	% sickling
Diggs et al. (1933)	Newborn	159	3.1
	11days-5yrs.	158	11.4
	6-10 yrs.	270	8.6
	11-15 yrs.	277	9.7
	16-20	115	11.2
Switzer (1950)	Newborn	211	8.5
	6-20 yrs.	843	15.4
	21-50 yrs.	1233	13.4
	51- yrs.	302	13.9
Neel (1951a)	12-20 yrs.	147	10.2
	21-50 yrs.	703	9.6
	51- yrs.	146	4.8

T A B L E 1 3

Variations in the Incidence of Sickling with Age: Africa and elsewhere

Region	Investig- ator	Age group	No. examd.	% sickling
West Africa	Findlay et al. (1946)	Newborn	25	36
		1-5yrs.	243	11.9
		6-15yrs.	455	9.6
		16-20yrs.	426	10.9
		21-50yrs.	1510	12.7
		60-yrs.	50	4
Nigeria	Jelliffe & Humphreys (1952)	0-14 days	51	0
		14days-lyr	120	25.0
		1-4yrs	60	23.3
		4-8 yrs	301	27.9
		8-15 yrs	512	25.0
		15-18yrs	144	20.9
		Young adults	641	21.5
		Older adults	52	26.9

Continued on next page

T A B L E 1 3 continued

Region	Investigator	Age group	No. examd.	% sickling	
Gold Coast	Colbourne et al. (1950)	0-lyr.	12	16.6	
		1-5yrs.	50	26.0	
		6-15yrs.	66	19.7	
		16-45yrs.	23	17.4	
		45-yrs.	255	22.4	
French W. Africa	Pales & Linhard(1952)	6-15yrs.	1350	6.2	
		15-yrs.	952	10.5	
Belgian Congo	Van den Berghe & Janssen(1950):	Baluba tribe	Children	155	15.5
			Adoles-		
			cents	374	23.8
			Adults	501	18.4
		Efe pygmies	Infants	32	25.0
			Children	87	21.9
			Adoles-		
			cents	46	30.5
			Adults	247	24.3
			Aged	44	38.6
		Mamvu tribe	Children	35	17.1
			Adults	163	21.4
			Aged	12	41.6
Belgian Congo	Parent (1950)	0-5yrs	314	31.52	
		5-15yrs	77	37.66	
		Adults	597	30.0	
Tanganyika	Mackey(1949)	Babies	433	16.4	
		Children	320	20.0	
		Mothers	283	23.3	
	Lehmann & Milne(1949)	Babies	21	33	
		Boys	60	25	
		Adults	172	25	
		Aged	41	32	
	N. Rhodesia (Balovale) (Ft. Jameson)	Beet(1946)	0-5yrs.	119	17.6
			5-yrs.	696	12.1
Beet(1947)		0-5yrs.	164	17.1	
		6-15yrs.	160	11.3	
		15-yrs.	965	11.2	

Continued on next page

T A B L E 1 3 continued

Region	Investig- ator	Age group	No. examd.	% sickling
Uganda	Lehmann(1951)			
	Sebei tribe:	Infants	5	0
		Children	21	0
		Adults	88	1
		Aged	10	0
	Bagishu tribe:			
		Infants	6	17
		Children	36	44
		Adults	142	27
		Aged	23	26
	Lango tribe:	Infants	19	37
		Children	57	30
		Adults	82	34
		Aged	18	39
Guadeloupe (French W. Indies)	Languillon (1951)	0-1yr.	25	0
		1-5yrs.	75	8.0
		6-15yrs.	680	6.4
		16-30yrs.	1180	8.8
		30-50yrs.	750	7.8
		50-yrs.	290	9.0

The number of babies in the series is given in parentheses in the column of mothers in each series.

tuberculous negroes in the Sea View Hospital, New York, showed an incidence of 5.3%, which is less than the average for the negro population of the United States.

T A B L E 1 4
INCIDENCE OF SICKLING IN MOTHERS AND THEIR BABIES

obtained a different result. They showed that 13%

Region	Investigator	Number of mothers	% sickling Mothers Babies	
New York	Watson et al. (1948)	226	3.4	8.0
Tanganyika	Mackey (1949)	233	23.3	16.6
Uganda	Lehmann (1951)	80	17.5	21.2

The number of babies is the same as the number of mothers in each series.

Several authors of sickle-cell surveys have divided their subjects into groups by age. Table 15 shows some of the more extensive results from America. Findings from Africa are set out in Table 16. Three investigations of the incidence of sickling in young babies and their mothers are summarized in Table 14.

There is little comparison to be made between some of the series, notably the American and those of West and of East Africa, as the latter

tuberculous negroes in the Sea View Hospital, New York, showed an incidence of 5.2%, which is less than the average for the negro population of the United States. This suggests that possession of the trait does not predispose to tuberculosis. Weiss and Stecher (1952) obtained a different result. They showed that 150 tuberculous patients at a general hospital had an incidence of sickling of 12.6%, whereas 150 non-tuberculous negroes attending the same hospital showed only 5.3%. The difference between the percentages is twice the standard error and is thus just significant. In a later paper Weiss (1953) suggests that the trait predisposes in the American negro to an acute exudative form of pulmonary tuberculosis.

Several authors of sickle-cell surveys have divided their subjects into groups by age. Table 12 shows some of the more extensive results from America. Findings from Africa are set out in Table 13. Three investigations of the incidence of sickling in young babies and their mothers are summarised in Table 14.

There is little unanimity in these findings. Some of the series--notably the American ones and those of Beet and of Findlay et al--show a decrease

in the incidence of sickling with advancing age. Those of Jelliffe and Humphreys, van den Berghe and Janssen, Pales and Linhard, Lehmann and Lehmann and Milne show no appreciable differences; while in Languillon's series the highest incidence is found in the aged. Where very young infants are examined the presence of foetal haemoglobin, which is very difficult to reduce, introduces a complication. This may account for the apparent absence of sickling in the newborn infants examined by Jelliffe and Humphreys, and for the low figures for babies found by the American investigators. Watson et al. (1948) have drawn attention to this phenomenon, and the difficulty was recognised by Lehmann and by Mackey in their investigations.

The decrease in the incidence of sickling with increasing age which some of the series show was remarked by Raper (1949). That sickling is not incompatible with long life was shown by Diggs et al. (1933) who discovered a sickler aged 99 years, as well as twelve who remembered the American Civil War. Neel (1951a) has considered the possible explanations of the decrease in incidence with age that some of the series show. If a real decrease

in incidence exists--and it is by no means agreed that it does--it may be due to differential elimination of bearers of the sickle-cell trait. I think this very unlikely; the point will be elaborated later. Neel has suggested two other possible explanations of the phenomenon. One is that the penetrance of the gene might increase with age; that is, that subjects whose cells do not sickle in their youth may show sickling as they grow older. This had in fact been suggested also by Raper (1949); but as both these authors observe, there is no evidence to suggest that it occurs. The other possible explanation advanced by Neel is that as most of the investigations have been done at least in part on hospital subjects, if trait-bearers should prove to be healthier than normal people they would be less represented in hospital populations as they grew older. The question of a positive advantage conferred by the trait will be dealt with in detail later; it is interesting to note that Raper (1949b) had again, though very tentatively, suggested the possibility.

(b) Direct Evidence

We have seen that there is no unanimity among workers who have investigated the incidence of sickling

in selected populations. In the direct study of sicklers and their outward characteristics, there is more agreement in those results that can be expressed statistically. Humphreys (1952) showed that there were no significant differences in weight and height between trait-bearers and normal subjects. Hiernaux (1952) could find no correlation between the presence of sickling and any of a number of anthropological measurements. Diggs et al. (1933), Lehmann and Milne (1949) and Neel (1951b) have examined haemoglobin levels in sicklers and non-sicklers and these authors agree in the finding that the trait is not associated with any degree of anaemia. Switzer and Fouche (1948) showed that the trait had no ascertainable effect on conception or pregnancy. Humphreys (1952) could find no appreciable differences between the hospital records of sicklers as compared with normal subjects in West African soldiers; he quotes no figures, however.

When we come to the opinions that various authors have expressed on clinical grounds, disagreement becomes marked. The view of Bauer and Fisher (1943), that the trait is a "biologic liability" has already been quoted, as has the similar view of Beet (1947). Raper (1949a) at first held this opinion, but later

(1949b) expressed the view that sickling in Africa is much less to be regarded as a cause of morbidity than in America. Wintrobe (1951) on the other hand regards the trait as having little clinical significance, a view that is shared by Sturgis in another haematological text. Steinberg (1930) observed that the trait was symptomless and did not shorten life, and Diggs et al. (1933) have already been quoted.

Of the investigations known to me, the only direct attempts to compare the health records of trait-bearers and normal subjects are those of Humphreys (1952), where the conclusions are stated without figures, and my own (Brain, 1952b) from which the results are quoted in the following chapter. These two investigations agree in the finding that the trait is not a cause of morbidity; my own results suggest further that possession of the trait may possibly confer a slight advantage in health over the normal subject (Brain, 1952a). This possibility was first suggested by Raper (1949b), but he regarded it as very unlikely. Neel (1951) pointed out that a positive advantage enjoyed by the trait-bearer would be the most likely alternative to the unduly high mutation rate that would otherwise have to be postulated, but

that the then available evidence was if anything against it. This will be elaborated later; but it is clear that on the subject of the effects of the trait all shades of opinion are represented; that it is a cause of morbidity, that it has no clinical effects, and even that it may confer an advantage in health.

Apart from these alleged general effects, the trait has been blamed for various specific manifestations, such as ulcers of the legs, thromboses and haemorrhages, and sudden death. It should be pointed out here that these effects undoubtedly do appear in sicklers; the question is simply whether they occur in true trait-bearers--i.e. heterozygotes--or whether they are in fact confined to those liable to sickle-cell anaemia. Before the difference between the trait and the anaemia was clearly recognised this distinction was not always drawn. Wintrobe (1951) clearly stated his view when he observed that "in association with the trait alone, neither anaemia nor the above symptoms (i.e. suggesting abdominal disease, rheumatic fever, osteomyelitis or neurological disorders) are produced." The principal specific effects which various authors have described are as follows.

Herrick (1910) in his description of sickle-cell anaemia noted that the disease was often associated with ulcers of the legs. In the trait-bearer, however, this complication does not occur with abnormal frequency (Diggs et al., 1933; Findlay et al., 1946; Adamson, 1951).

Findlay et al. (1946) investigated the question whether the jaundice which occurs in about 10% of African natives with pneumonia (Gelfand and Lewis, 1942) is correlated with sickling. They found no significant difference in the incidence of this jaundice between sicklers and non-sicklers.

Most of the specific effects which the trait is alleged to produce are the results of vascular obstruction. There is no doubt that in homozygous sicklers such effects occur. Bauer (1940) and Bauer and Fisher (1943) believe that in sickle-cell anaemia the anaemia itself is a secondary effect due to the haemolysis of masses of sickled cells which have become impacted in small vessels by reason of their shape. This view offers a unitary theory of sickle-cell disease in all its manifestations. Bauer believes that the primary event is the in vivo sickling of red cells, due for example to anoxia. This may result either

in vascular phenomena such as thromboses, haemorrhages or sudden death, or in a haemolytic anaemia due to the disintegration of these impacted cells. Bauer and Fisher believe that all carriers of the trait are liable to these alarming complications. Beet (1947) has suggested the possible importance of infections, and of anaemias not primarily due to sickling, in reducing the oxygen tension in the body and thus starting off the sickling process in vivo. He thinks infarcts of the spleen particularly common and reports a case of perisplenitis which he regards as due to splenic infarction resulting from sickling. Gelfand (1950) regards the sickling in these cases as coincidental. Beet observed that bearers of the trait showed a lower proportion of palpable spleens than normal subjects, and regarded this as evidence that the spleen in sicklers was usually small as a result of repeated infarctions. As we shall see later, there are other possible explanations for this phenomenon. Beet believes that local infections such as abscesses have more serious effects in sicklers than in non-sicklers, because the reduced oxygen tension encourages local sickling and the resulting stasis further diminishes the blood supply.

These thrombotic attacks may give rise to diverse manifestations. Thompson et al. (1948) have recorded a case of death following coma in a non-anaemic sickler, proved at autopsy to be due to cerebral thromboses and haemorrhage. Other cases of this kind in the non-anaemic have been described by Bauer (1940) (massive necrosis of renal cortex); Abel and Brown (1948) (haematuria and a condition simulating renal neoplasm); Bronstein (1951) (subarachnoid haemorrhage in a child); and Green and Conley (1951) (Multiple areas of cerebral thrombosis). Murray-Lyon (1944) observed that sickle-cell disease must always be considered in the differential diagnosis of cerebral symptoms, pains in the bones and joints, abdominal pain and leg ulcers in Africans. Several authors have described cases of sudden death in apparently healthy sicklers; in West Africa this is apparently particularly common in pregnant women, though anaemia may be a feature of the attacks (Robertson and Findlay, 1947; Edington, 1951). Raper (1949a) has described cases of sudden death due apparently to sudden massive sickling of red cells. Flying at high altitudes may possibly be dangerous to sicklers because of the low oxygen tension. Findlay et al. (1947) examined

three Africans with the sickle-cell trait after 15 minutes at an altitude of 15000 feet. All showed the presence of a proportion (0.8 to 5%) of sickled cells in the circulating blood, but there were no pathological effects. Henderson and Thornell (1946) in America found no change in three negroes with the trait who were tested in a low-pressure chamber at the equivalent of 15000 feet altitude; one with sickle-cell anaemia showed an increase of intravascular sickling from 8 to 15% without pathological effects. Sullivan (1950) observed a patient, said to be a trait-bearer and previously well, who after a long flight at between 10000 and 16000 feet developed splenic enlargement and electrocardiographic abnormalities. He suggested that the long period of exposure to low oxygen tension might have been significant in this case.

quite clear that some mechanism, the nature of which is not altogether clear, is keeping up the gene frequency.

We may consider first the advantages of the selective disadvantages in which homozygous individuals are liable. It seems probable that the homozygous sickle-cell anaemia occurs in the great majority of individuals

POPULATION GENETICS OF SICKLING

Sickling is due to a dominant gene which when present in the homozygous state often has early fatal effects, either from sickle-cell anaemia or other pathological manifestations. In this way a proportion of the total sickling genes in the population is lost in each generation, and one would expect the incidence of sickling to decline from one generation to the next until the gene disappeared altogether. The sickling gene, however, shows no sign of dying out. In the Baamba, for example, the incidence of sickling is now 45%; if it is in the process of disappearing it must have had initially a truly astonishing incidence. And if the mechanism is solely one of loss of some genes in each generation, it is hard to see how an incidence of this magnitude could ever have been established. It is quite clear that some mechanism, the nature of which is not altogether clear, is keeping up the gene frequency.

We may consider first the magnitude of the selective disadvantage to which homozygous sicklers are liable. It seems probable that in America sickle-cell anaemia occurs in the great majority of individuals

homozygous for the gene and that the affected individuals usually die before reaching reproductive age. Those who survive have a fertility of only about 20% of the normal (Neel, 1951). This makes it clear that in America at any rate the homozygous sickler labours under a heavy selective disadvantage. In Africa the question is more controversial. It was at first believed by most investigators that sickle-cell anaemia was rare in Africa, even in parts where the sickle-cell trait was present in high proportions. Foy, Kondi and Brass (1951), however, showed that in the Jaluo tribe of Kenya sickle-cell anaemia occurred to the extent expected from the genetic theory of Neel and Beet, and that most of the affected individuals died in infancy. An extensive study by the Lambotte-Legrands (1951) in the Belgian Congo led to the same conclusion. Such findings are not by any means universal, however. In other parts of Africa experienced investigators on the lookout for sickle-cell anaemia are of the opinion that it occurs but rarely. Thus Lehmann (1951) thinks that numerous homozygotes must survive in Africa without developing the anaemia, and quotes an isolated population in Uganda in which 46 of 53 individuals examined showed sickling. As he observes,

this makes it very likely that homozygous sicklers are reproducing here. Again, in the Baamba tribe the proportion of 45% sickling would be remarkable if it did not include homozygotes. Jelliffe (1952) in West Africa, and Mackey (1949) in Tanganyika find the same rarity of sickle-cell anaemia in populations with a high incidence of sickling. Raper (1950) has gone so far as to suggest that admixture with non-negro strains is necessary for the production of sickle cell anaemia. This would account for its frequency in the American negro. Some supporting evidence from America has been provided by Hodges (1950), who found that the incidence of sickling was higher in individuals of mixed stock than in apparently pure negroes. The Black Caribs of Honduras, a negro people who have suffered no admixture of foreign blood, have a high incidence of sickling but do not develop sickle-cell anaemia (McGavack and German, 1944). The fact that sickle-cell anaemia does apparently occur in some exclusively Bantu tribes in the expected proportions casts doubt on this theory, however. An annotator in the British Medical Journal (1952, ii, 433) has suggested that neither of the opposing views may be wrong. He thinks that the incidence of sickle-cell

anaemia in homozygous sicklers may vary from place to place in Africa, controlled perhaps by other genetic factors influencing the amount of abnormal haemoglobin possessed by homozygotes. This seems, from the evidence, to be extremely probable. On the other hand, if

It is at any rate clear that in America and some parts of Africa a large proportion of homozygotes is eliminated by the anaemia before reaching reproductive age. Even in the areas where sickle-cell anaemia is uncommon it has never been suggested that it is absent. In Africa the homozygous sickler thus suffers a selective disadvantage, which although it may vary from place to place is sometimes at any rate considerable. We must now consider the various mechanisms by which the gene frequency could be maintained. Neel (1951a)

The first and most obvious of these is mutation. Some of the inherited diseases, such as haemophilia, are certainly eliminated by selection, and their incidence in the population is governed by the low rate at which the genes can be replaced by mutation--that is, by the appearance of the gene de novo in the chromosomes of normal individuals. All these conditions known to be replaced by mutation are relatively rare. As for sickling, as Neel (1951a) observes with reference to

thalassaemia, if the gene is being replaced by mutation we have to account for the fact that this mutation is confined to certain stocks; for example, while occurring in American negroes it is practically never seen in white Americans. On the other hand, if sickling has some adaptive significance by virtue of which it is perpetuated, one can readily account for its restricted geographical distribution and need only invoke mutation to account for the original appearance of the gene on one occasion in the past. Though in the American negro with his relatively low and more or less constant rate of sickling, some case might be made for replacement by mutation, in Africa it seems unlikely that this is the mechanism. In a tribe with an incidence of sickling of 30%, as Neel (1951a) has shown, homozygotes could only be replaced by a mutation rate of 1×10^{-2} , which is an incredibly high figure. Haldane (1948) has shown that the rate of mutation in man, where it has been measured, lies between 4×10^{-5} and 4×10^{-6} per gene locus per generation. In addition, if the sickling gene is being replaced by mutation, the rate of mutation would have to be different in almost every tribe, since all gradations of incidence from 0.6% to 45% occur.

Another mechanism that might act in keeping up the gene frequency is mentioned by Neel (1951a). An abnormal genetic mechanism which resulted in an increase in the proportion of heterozygous sicklers over that expected would have this effect; but as Neel points out, no such effect has ever been observed.

As Neel observes, the most logical alternative to mutation is the existence of positive selection in favour of the heterozygote. This would mean that the trait-bearer enjoyed some advantage over the normal individual. This had been tentatively suggested by Raper (1949b) who observed that it was not at all likely. Neel (1951a) though regarding it as the most likely alternative to mutation, admitted that the then available evidence was if anything against it, because of the decline in sickling incidence with age that most of the surveys reviewed by him showed. (See Table 12, which contains the American material cited by Neel).

This would suggest that trait-bearers suffered a disadvantage and were being selectively eliminated, though there are other possible explanations. As we have seen, however, this decrease in incidence with age has not been found by all investigators, and one (Lan-guillon, 1951) has found an increase with increasing

own findings, is considered in the section of discussion.

age. Foy and Kondi (1951) have suggested that the mechanism may be one of increased fertility in bearers of the trait. Silvestroni et al. (1950) have shown that in the related disease of Mediterranean anaemia an advantage in fertility does seem to be possessed by the heterozygote. Foy and Kondi have further suggested that an advantage in fertility enjoyed by heterozygotes might be reinforced by selective mating between sicklers--that is, that individuals with the trait might be more liable to mate with other sicklers than with normal subjects. This is discussed later.

The alternative to an advantage in fertility on the part of the trait-bearer,--with which indeed it might well coexist--is as we have seen an advantage in resistance to disease enjoyed by the heterozygote. In the previous chapter it has been shown that the clinical status of the trait-bearer is a matter of controversy. As far as I know, my own results (see following chapter) are the only ones that offer any direct evidence, however inadequate, for the view that the heterozygous sickler enjoys a selective advantage. There is no other direct evidence either for or against the theory. This question, dealing as it does with my own findings, is considered in the section of discussion.

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EFFECTS AND POPULATION GENETICS OF THE SICKLE-CELL TRAITCHAPTER VI
ORIGINAL WORK

The material and the techniques used in this part of the work are the same as those used in the first part, and have already been described. This chapter describes investigations of sickling incidence in hospital admissions and fit men, and studies in sicklers and non-sicklers of hospital records, spleen rates, body weight and fertility.

1. Incidence of Sickling in Fit Men and Hospital Admissions. In this part of the work a consecutive series of 1194 bloods was examined at Shabani; this included all admissions to hospital during the period and all fit men seen during the same time. Of the total number, 923 were fit men and 464 were hospital admissions. Of the hospital patients, 193 were admitted to medical wards; the remaining 271 were admitted with injuries, minor surgical conditions, and venereal diseases. Table 15 shows the incidence of sickling in these groups; there is no significant difference between the incidences in any of them.

TABLE 15

Incidence of Sickling in Fit Men and Hospital Admissions

Group	Number examined	Number sickling	% sickling	Differ- ences	Standard errors of diffs.	Diff. S.E.
A. Medical Admissions	193	6	3.11	B-A 0.95%	1.8	0.5
B. Non-medical admissions (Injuries, minor surg- ical, and venereal dis- eases)	271	11	4.06	C-A 0.57%	1.5	0.4
C. Fit men	923	34	3.68	C-D 0.02%	1.1	0.02
Total (A B C)	1337	51	3.68	E-A 0.66%	1.5	0.5
D. All hospital admissions (A B)	464	17	3.66			
E. Fit men and non-medical admissions (B C)	1194	45	3.77			

2. Hospital Records of Sicklers and Non-Sicklers.

In this investigation the hospital records of fifty sicklers--with one exception the first fifty discovered at Shabani--were compared with those of a control group of non-sicklers. The one subject excluded was one for whom no satisfactory control could be found, but was not in any other way remarkable. The population of mine workers has many advantages for an investigation of this kind. It is served by a single hospital, and this is the only hospital to which mine workers are admitted. The hospital records have been carefully kept for thirty years. A native who does not attend his work because of illness or injury is automatically admitted to hospital; thus the records reflect faithfully all disorders serious enough to interrupt work.

In Table 16 the complete hospital records of the 50 sicklers have been totalled up and compared with those of a control group constructed as follows. Using a list of known non-sicklers, each sickler was paired off with a non-sickler of the same (or occasionally a closely related) tribe, having approximately the same length of service with the company. Wherever possible one engaged in the same month, or at any rate

Hospital Records of Sicklers and Non-Sicklers

Reason for admission	Sickling Group		Control Group	
	50 individuals:	total days74164	50 individuals:	total days70822
	Days in	% of	Days in	% of
	hospital	total	hospital	total
MEDICAL				
Amoebic dysentery	31		0	
Arthritis	7		0	
Avitaminoses	37		13	
Bilharziasis	49		24	
Chest diseases:				
Bronchitis and				
influenza	75		70	
Pneumonia	157		141	
Congestion	0		35	
Tuberculosis	12		84	
Debility	32		0	
Malaria and P.U.O.	29		90	
Minor conditions:				
Chickenpox	0		7	
Conjunctivitis	4		26	
Coryza	15		0	
Headache	5		6	
Iritis	0		15	
Myalgia	7		31	
Pharyngitis	7		17	
Pleurodynia	6		0	
Scabies	34		0	
Stomatitis	0		14	
Torticollis	5		0	
Unclassified	7		0	
SURGICAL				
Abscesses	0		31	
Boils	23		0	
Cellulitis	0		4	
Leg ulcers	0		20	
Tenosynovitis	16		14	
INJURIES AND V.D.				
	924		1027	
TOTAL MEDICAL	519	0.70%	573	0.81%
CHEST DISEASES	244	0.33%	330	0.47%
TOTAL SURGICAL	39		69	
GRAND TOTAL	1482	2.00%	1669	2.36%

within a month or two of the sickler, was chosen. With a few sicklers of very long service such close approximation could not be obtained. This makes for approximate equality of age in the two groups; very exact agreement cannot be attained since very few natives have the least idea of age. More important, it ensures that each control subject has served during the same period as the corresponding sickler, and thus periodical and seasonal variations in the incidence of disease do not affect the validity of the results. To avoid "psychological selection" in the compilation of the control group, the hospital records of the non-sicklers were not examined until after the composition of the group had been decided.

The 50 sicklers had periods of service varying from 10 days to 8806 days with a mean of 1483 days and a standard deviation of 2452 days. The control group of 50 non-sicklers had service varying from 10 days to 8725 days, a mean of 1417 days, and a standard deviation of 2319 days. The totals of service were 74,164 days (about 200 years) for the sicklers and 70,822 days for the non-sicklers.

The results (Table 16) show that in every main group of disorders the sickling group spent less time

in hospital than did the non-sicklers, and this despite the fact that the sickling group have a greater aggregate length of service. There is no simple or entirely reliable means of assessing the significance of the observed differences.

3. Spleen rates in Sicklers and Non-Sicklers.

Spleens were palpated for in the ordinary way with the subjects recumbent, and the spleens reported simply as palpable or not palpable. Care was taken to see that the composition of the non-sickling group was as nearly as possible the same as that of the sickling group in all respects, such as tribe and length of service. This was achieved by examining groups of similar subjects--e.g. recruits from Nyasaland--for palpable spleens before inspecting the blood samples, thus eliminating psychological bias. Patients admitted to hospital for diseases which might affect the size of the spleen were not included in the series. The results are in Table 17, and show that the spleen is palpable in a significantly lower proportion of sicklers than non-sicklers.

4. Weights of Sicklers and Non-Sicklers.

Every employee is weighed on engagement. A group of 76 sicklers was compared with a control group of 76 non-

sicklers of similar tribe and length of service, constructed in exactly the same way as the control group of Table 16.

TABLE 18

Weights of Sicklers and Non-Sicklers

TABLE 17

Spleen Rates in Sicklers and Non-Sicklers

Non-Sicklers

	Number examined	Number with palpable spleens	% with palpable spleens
Sicklers	90	24	26.67
Non-Sicklers	614	233	37.95

Difference between percentages 11.28%.

Standard error of difference 5.44

Difference / S.E. 2.07.

sicklers of similar tribe and length of service, constructed in exactly the same way as the control group of Table 16.

TABLE 18

Weights of Sicklers and Non-Sicklers

	Number examined	Range, lbs.	Mean, lbs.
Sicklers	76	90 - 165	124.7
Non-Sicklers	76	87 - 153	124.6

The very close and somewhat suspicious similarity of the means in the two groups is the result of chance.

5. Fertility of Sicklers and Non-Sicklers. The material available to me does not allow of a decisive investigation of this problem. To show a significant difference of 2% between the sizes of families in sicklers and non-sicklers would need samples of several thousand of each. Nevertheless, since no such investigation has to my knowledge been attempted before, it is worth while to see whether any startling difference in fertility exists between sicklers and non-sicklers. This is of particular interest since Foy and Kondi (1951) have suggested that increased fertility

in sicklers may be one of the mechanisms by which the gene frequency is kept up.

The investigation was organised as follows. Adult subjects were questioned at the time of taking blood to ascertain the numbers of live children born to their mothers. It would have been interesting to obtain details of abortions and stillbirths, but it was soon clear that such information could not be relied on. Bearers of the sickle-cell trait must have at least one sickling parent; but normal subjects may have one or even both parents bearers of the trait. Short of examining the parents of all the normal subjects there is no way of allowing for this; but the proportion of sicklers in the parents of the sickling group is obviously at least 50%, and must be much higher than in the parents of the non-sickling group. The object in questioning adults about the numbers of their siblings, and not of their children, was to consider families which had as far as possible completed their production of children. Any subject who showed hesitation in replying was excluded. Occasionally a native will deliberately fabricate when questioned by Europeans on seemingly irrelevant matters; this introduces a complication

that cannot be allowed for, but there is no reason to suppose that sicklers are more liable to it than are normal subjects. It seems plain from the results (Table 19) that at any rate no very remarkable difference in fertility exists between the sicklers and non-sicklers in my population.

TABLE 19

Sizes of Families (Live births) from which adult sicklers and non-sicklers are drawn

	Total				
	Number	Live births	Range	Mean	S.D.
Sicklers	96	521	1-10	5.427	2.04
Non-Sicklers	586	3237	1-17	5.524	2.62

The difference between the means is 0.097, which is 0.41 times the standard error of the difference. This is not a significant difference.

EFFECTS AND POPULATION GENETICS OF THE SICKLE-CELL TRAIT

CHAPTER VII

DISCUSSION

EFFECTS OF THE SICKLE-CELL TRAIT

From the results

in the previous chapter, it is quite clear that in the population examined by me the sickle-cell trait has no discoverable ill effects, either general or specific. As far as comparison is possible, the incidence of the trait in my selected population of fit mine workers appears to be the same as in the tribes at home, if indeed it is not somewhat greater. This is an important finding, because my population is a highly selected group and it might be argued that only the healthier sicklers are represented in it. The incidence of the trait in patients admitted to hospital is not greater--indeed it is somewhat less--than in fit workers, and amongst the hospital admissions the lowest incidence of sickling is in fact observed in those admitted to medical wards. None of the differences is statistically significant, however. The trait is without influence on body weight. When the hospital records of sicklers and non-sicklers are compared it is seen that the sickling

group, in spite of possessing a greater aggregate length of service than the non-sicklers, spent less time in hospital with every main group of disorders than did the non-sicklers. This makes it clear that in this population at any rate the sickle-cell trait is not a cause of morbidity, and the findings bear out the clinical impression that sicklers are not abnormally liable to disease. For example, a trait-bearer has been employed continuously in the hospital for over 25 years without losing a day's work from illness, though it has been suggested that his position as head dispensary orderly may have given him unusual opportunities for self-medication! The results in fact suggest that the possession of the trait may confer a slight advantage in resistance to disease. This will be considered later.

The finding that the sickle-cell trait does not predispose to disease is not in accord with the views of Bauer and Fisher (1943), Evans (1944), Beet (1947) and others who have regarded the trait as a cause of morbidity. Of these authors, the only one producing statistical evidence is Evans (1944) who found a highly significant increase in sickling incidence in hospital patients as compared with normal subjects.

I have suggested (Brain, 1952b) a possible explanation of this finding, as follows. For some reason, adult cases of sickle-cell anaemia seem to be commoner among the non-Bantu West African negroes, from whom the American negro is also derived, than in the Bantu tribes. Several cases of sickle-cell anaemia and the sickling crisis in adult West African negroes have been published by Robertson and Findlay (1947), Evans (1945), Edington (1951), Reid (1936) and others. In the Bantu, adult cases of sickle-cell anaemia are, to judge by the literature, very rare; this has also been remarked by Vandepitte (1952b). At Leopoldville in the Belgian Congo, only one adult case had been seen up to the end of 1951, though many had been found in children. Foy, Kondi and Brass (1951) in Kenya find almost all their cases of sickle-cell anaemia in infants, though Foy et al. (1952) observed one in Portuguese East Africa in a subject of 18 years. An adult case has been observed in a native of Nyasaland by Osburn (unpublished). It is conceivable that the difference between the West African negroes and the Bantu may be a genetic one affecting the severity of the disease in the homozygous sickler. At all events it does seem probable that adult cases of sickle-cell anaemia are commoner in the West Africans

than among the Bantu. It seems likely that in Evans' series of West Africans the hospital patients included a proportion of adult homozygous sicklers. These homozygotes are liable to sickle-cell anaemia, and even if not admitted for anaemia at the time of the investigation, they are certainly unduly liable to intercurrent disease. I think it probable that in Evans' series the issue has been confused by the presence among the hospital admissions of both trait-bearers and homozygous sicklers. The same explanation may be applied to the findings of certain authors already reviewed, that children show a higher incidence of sickling than adults. Where this occurs it may be due to the presence in the lower age groups of homozygous sicklers who are selectively eliminated as time goes on, and not to selection operating against bearers of the trait. I have suggested this elsewhere (1952b). As we have seen, the finding of the highest sickling incidence in the young is far from universal; at least one author finds the incidence to be highest in the aged (Languillon, 1951) and many no change in the incidence with age. There is no doubt at all that homozygous sicklers do occur in the lower age groups, and that they are selectively

eliminated as time goes on; the only question is whether they are numerous enough at the beginning of life to account for the considerably higher incidence in children found for example by Findlay et al. (1946). In view of the finding that adult trait-bearers are not abnormally prone to disease, it seems very unlikely that heterozygous sicklers are selectively eliminated.

The views of Bauer and Fisher (1943) and of Beet (1947) are more difficult to answer, being based on clinical impressions rather than figures. I can only observe that my own clinical impressions, which are supported by statistics, do not agree with theirs. There is no doubt that almost any conclusion can be drawn from a study of small samples. The sickle-cell trait may coexist, quite fortuitously, with any combination of congenital or acquired defects, and two or three cases of this kind may give a strong clinical impression that the trait is a cause of morbidity. Bauer and Fisher observed American cases, among whom as we have seen it is conceivable that there may have been a proportion of homozygous sicklers, not necessarily anaemic. In African patients, as Gelfand (1944) has observed, several unrelated diseases more often than not coexist, and the sickle-cell

trait may thus be blamed for manifestations in which it in fact plays no part. Beet's view that trait-bearers are abnormally liable to abscesses, infarctions and local infections is not borne out by my results.

The only other statistically supported claim known to me for the trait as a cause of morbidity is that of Weiss and Stecher (1952) who maintain that possession of the trait predisposes to tuberculosis. This is not borne out by the earlier investigation of Dolgopol and Stitt (1929), and the difference in incidence observed by Weiss and Stecher is only just significant and thus not very unlikely to have arisen by chance. Plainly the possession of the trait is not the only reason for the negro's low resistance to tuberculosis, since tribes with a very low incidence of sickling, such as the Karanga of Southern Rhodesia, are very liable to the disease. Nevertheless the point needs further investigation. It is more than probable that, under certain specific circumstances, the possession of the trait is disadvantageous, and exposure to tuberculosis may be a circumstance of this kind. This is not meant to imply that the trait on the whole confers a disadvantage. There is probably no generally advantageous characteristic, either hereditary or acquired, which does not in certain special

circumstances prove disadvantageous. In the same way, generally undesirable conditions may in certain circumstances confer some advantage, as for example mitral stenosis in increasing the resistance to pulmonary tuberculosis. I am convinced that the sickle-cell trait is not a predisposing factor to morbidity in general, as sickle-cell anaemia undoubtedly is; it is not by any means certain, however, that in certain special circumstances it may not predispose to specific diseases. It is very clear on biological grounds that if the gene frequency is not being maintained by mutation--and we have seen that it almost certainly is not--then a general selective disadvantage associated with the sickle-cell trait is out of the question; there then would be no imaginable mechanism that could save the gene from extinction. This will be further considered later; but it is plain that on evolutionary grounds views such as those of Bauer and Fisher (1943), that the trait-bearer is at a general disadvantage in health, must be regarded with suspicion.

It has been shown that in the population examined by me the sickle-cell trait does not predispose to morbidity, and that on biological grounds this is what would be expected. There is no doubt, however,

that sickle-cell anaemia and other catastrophes do occur in some of those with sickle-cells. It seems clear that, with rare exceptions, sickle-cell anaemia is confined to those homozygous for the sickling gene (Neel, 1949). Despite the views of several authors to the contrary, it seems to me likely that the other complications of sickling, arising from vascular obstruction by sickled cells, are in the same way confined to homozygotes and do not, except perhaps very rarely, occur in bearers of the trait. The view of Wintrobe (1951), with which I am in entire agreement, has already been quoted, that "in association with the trait alone, neither anaemia nor.....symptoms are produced." A consideration of the specific effects observed in certain sicklers further bears it out:

Bauer and Fisher (1943) and Bauer (1940) have offered a unitary theory of sickle-cell disease in all its manifestations, by which the primary lesion in all cases is an impaction of sickled cells in small vessels, and the anaemia is secondary to the disintegration of these cells. There is some doubt whether this is the true explanation of the haemolysis in sickle-cell anaemia. Cases frequently

present with anaemia unassociated with vascular symptoms, and Reinhard et al. (1944) have shown that in patients with sickle-cell anaemia, breathing oxygen reduces the degree of intravascular sickling but has no effect on the rate of haemolysis. The question is fully reviewed by Singer (1951). The mechanism of haemolysis, however, is not material to the argument. It seems fairly clear that the other manifestations--the thromboses, infarctions and haemorrhages--are indeed the results of intravascular sickling of red cells. The question is simply whether such intravascular sickling occurs to any significant degree in trait-bearers as distinct from homozygous sicklers.

It has for some time been recognised that as a practical measure for differentiating the anaemia from the trait, the presence of sickled cells in the ordinary blood smear has diagnostic value. Vande-pitte and Pieters (1952) and Pales and Linhard (1952) state that sickled cells are never seen in ordinary smears taken from the peripheral blood of trait-bearers, and this is confirmed by my own experience. This suggests that intravascular sickling, at any rate in accessible vessels, does not occur in trait-bearers under ordinary conditions; abnormal conditions, such

as flying at high altitudes, may as we have seen sometimes produce them. The electrophoretic studies of Pauling and his colleagues (1949) have shown that in most cases of sickle-cell anaemia all the haemoglobin in the cells is of the abnormal variety, very insoluble when reduced; whereas in trait-bearers there is a considerable proportion of normal haemoglobin. Intravascular sickling thus occurs at much less reduced oxygen tensions in homozygous sicklers than in trait-bearers, since even a small proportion of normal haemoglobin in the cells greatly increases the total solubility. It has been shown (Neel et al., 1951) that genetic factors influence the amount of abnormal haemoglobin possessed by both homozygotes and heterozygotes, but for practical purposes the homozygous sickler always possesses a much higher proportion of this abnormal haemoglobin than the trait-bearer, and frequently all his haemoglobin is of the abnormal variety (Pauling et al., 1949). Occasionally a heterozygote might inherit enough of the abnormal haemoglobin to produce clinical manifestations, but this must be a rare event if it occurs at all.

We have already seen that Bauer (1940) regards the haemolysis in sickle-cell anaemia as a result of

the disintegration of sickled cells which have become impacted in small vessels. If this view is correct, then it is clear that intravascular sickling marked enough to lead to haemolysis does not occur at all in trait-bearers; it has been repeatedly shown that the sickle-cell trait is not associated with any degree of anaemia, however slight.

It is of course by no means certain that all homozygous sicklers possess enough of the abnormal haemoglobin to make them liable to intravascular sickling. It is very probable indeed, however, that the clinical effects which do appear are for practical purposes confined to homozygous sicklers, whether anaemic or not; and that they do not occur in trait-bearers except perhaps with extreme rarity.

Several authors have published reports of autopsies at which small vessels were found stuffed with sickled cells, and the sickling crisis has been invoked as the cause of death. Several cases of this kind are mentioned in a previous chapter (Chapter V), and Raper (1949a) has reported a series. While I do not mean to imply that in all or any of these cases the sickling was a post-mortem effect, the following case is perhaps instructive. It shows that sickling can occur rapidly after death, and in it, were it not

for the blood smear taken during life, intravascular sickling would have been regarded as a major factor leading to death:

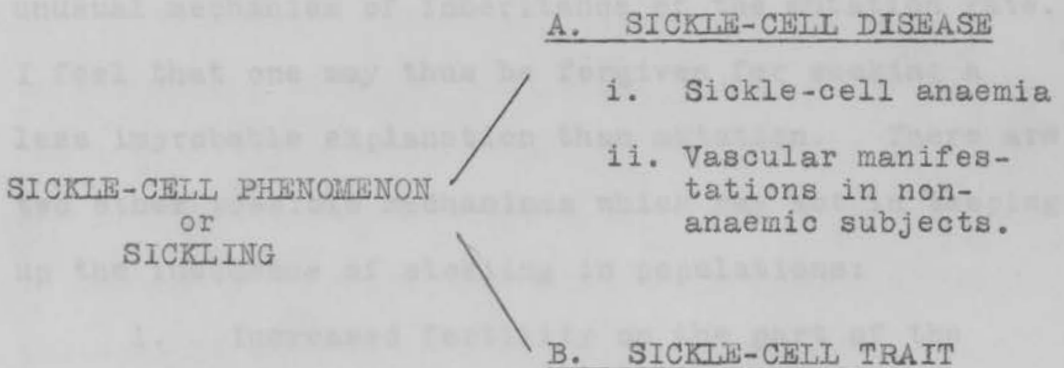
CASE REPORT A young adult male of the Nyakyusa tribe, a known sickler, was admitted to hospital in coma in the early hours of the morning; friends stated that he had complained of generalised pains for the past twelve hours. He was seen by the medical officer on duty, who observed mild pyrexia and Cheyne-Stokes respiration; a blood smear was taken but the patient died before it could be stained. Autopsy was carried out seven hours after death. At this stage, blood aspirated from the right ventricle and immediately sealed under a coverslip showed 100% sickling, with the characteristic filamentous processes of sickle-cell anaemia beginning, it was thought, to develop. The only other abnormal finding was a small amount of thin exudate at the base of the brain. The spleen showed no abnormality and no signs of old infarctions. The diagnosis made at autopsy was one of the sickling crisis--death in the non-anaemic from massive intravascular sickling. The smear made during life was then stained and examined, in the expectation of seeing abundant sickle-cells. Despite a careful search none were found, the only abnormality noticed

"sickle-cell disease" should be retained, since

being an increase in polymorph leucocytes. Histological examination of the brain showed an acute meningitis, which was the cause of death. All the vessels in all the organs examined (brain, liver, kidneys and spleen) contained sickled cells. There was no doubt that all the sickling in this case was a post-mortem effect, though its rapidity was somewhat surprising when compared with the rate usually observed in sealed coverslip preparations. Unless autopsies on sicklers are performed immediately after death such post-mortem sickling may well confuse the issue.

We have seen that my own results provide no support for the view that the sickle-cell trait predisposes to morbidity. If it is true, as I think, that the trait is not a pathological state, a change in the terminology of sickling would be desirable. Originally the distinction was drawn between sickle-cell anaemia and the sickle-cell trait. Bauer and Fisher (1943) and Beet (1947) would prefer a single category, sickle-cell disease, since as they justly observe, severe and even fatal manifestations may occur in the absence of anaemia. Both these authors believe that all trait-bearers are liable to complications. It is plainly desirable that the term "sickle-cell disease" should be retained, since

anaemia is only one of the pathological manifestations of homozygosity for the sickling gene. I would suggest, however, that the term "sickle-cell disease" should not embrace the sickle-cell trait, since the trait-bearer is not suffering from a diseased state. The general term "sickle-cell phenomenon" or simply "sickling" might be used to embrace all the conditions characterised by sickling of the red cells. It could be subdivided into (a) sickle-cell disease, to include sickle-cell anaemia and vascular manifestations in the non-anaemic, and (b) the sickle-cell trait, a symptomless, non-pathological except genetically^x, and possibly even beneficial state. The classification might be graphically represented thus:



^x In that the trait-bearer, by mating with another trait-bearer, may produce children with sickle-cell disease.

POPULATION GENETICS OF SICKLING

We have seen that

homozygous sicklers, or at any rate a proportion of them, labour under a considerable selective disadvantage. It seems fairly clear also that mutation is not the mechanism by which the gene frequency is kept up. However Hiernaux (1952) has suggested that this is accomplished by mutation. He suggests that the rate of mutation is genetically controlled, the tribes with a high rate of sickling inheriting also an increased tendency towards mutation from the normal to the sickling gene. This is an ingenious suggestion. The rate of mutation that would be necessary, however, in a tribe of high sickling incidence--say 30% or more--is astonishingly high, to say nothing of the somewhat unusual mechanism of inheritance of the mutation rate. I feel that one may thus be forgiven for seeking a less improbable explanation than mutation. There are two other possible mechanisms which may act in keeping up the incidence of sickling in populations:

1. Increased fertility on the part of the heterozygote or trait-bearer. Foy and Kondi (1951) have further suggested that this increase in fertility may be augmented by selective mating between trait-bearers.

2. An advantage in health enjoyed by trait-bearers over normal people, making them less liable to elimination by disease.

These possible mechanisms--which, it may be added, are not necessarily alternative--will be considered in turn.

1. Increased fertility in heterozygotes. This mechanism has been suggested by Foy and Kondi (1951). In the related condition of thalassaemia this increased fertility in heterozygotes does appear to exist; Silvestroni et al. (1950) have shown that matings of two heterozygotes are more fertile than those between heterozygote and normal or between two normal subjects. As Neel (1951a) observes, this effect may be a result of civilisation. Heterozygotes in thalassaemia suffer from a clinical condition, thalassaemia minor, and are mildly anaemic (Neel, 1951a); it is hard to see how this can contribute directly to an increase in fertility. A psychological mechanism, I would suggest, is more probably at work. Race and Sanger (1950) have described such an effect in acholuric jaundice and erythroblastosis foetalis. They observe that in human families deaths in infancy are usually over-compensated by an increased number of births,

so that, for example, mothers with acholuric jaundice are found to have a larger number of surviving children than normal subjects have in spite of having had an abnormally high number of stillbirths and neonatal deaths. The reasons for this effect, which has not been observed in sicklers but might well occur, are apparently psychological and physiological.

It is quite probable that an increased fertility does occur in heterozygous sicklers, though my own results--which are however very inadequate--provide no support for the view. That it is the only mechanism at work is very unlikely. In a population with a low incidence of sickling the gene frequency might perhaps be maintained by such a mechanism. As an annotator in the British Medical Journal (1952, ii, 433) observed, however, it is hard to imagine an increase in fertility that could replace the loss of homozygotes in a population of high sickling incidence. If we take as an example the Makonde of Portuguese East Africa, in whom Foy et al. (1952) found an incidence of sickling of 40%, it is clear that the increase in fertility would have to be very great to maintain the frequency from one generation to another. Assuming, as Foy, Kondi and Brass (1951)

and the Lambotte-Legrands (1951) believe, that all homozygous sicklers die young, we may make a rough calculation as follows. With this incidence in the adult population, every 100 pregnancies should consist of approximately 8 homozygous sicklers with the genetic constitution SS, 37 heterozygotes (Ss) and 55 normal subjects (ss). If all 8 of the SS children are eliminated before they can reproduce, all the S genes in the adult population--about 18.5% of the total S and s genes--will be carried by heterozygotes. These heterozygotes must then not only maintain in the next generation the frequency of 18.5% S genes but must provide by their increased fertility an additional 3% of S genes to replace the loss of homozygous sicklers. This would require an increase in fertility of nearly half as much again as normal subjects.

Foy and Kondi (1951) and Foy, Kondi and Brass (1951) have suggested that the effect of increased fertility in heterozygotes might be increased by selective mating between sicklers. It is not quite clear how this could come about. There is no known method, short of examining the blood, of identifying the Ss genotype in a prospective mate; sickling in this

respect differs from thalassaemia, in which heterozygotes suffer from a clinical condition. If it is meant that the trait-bearer is more likely to mate within his own tribe than with a member of another tribe of lower incidence, this is so; but the outside tribe might equally well be one with a higher incidence of sickling. The only other way in which selective mating might take place would be through the prevalence of matings between closely related persons, but these are frowned on in almost all savage tribes.

The psychological mechanism described by Race and Sanger and already referred to may well have the effect of increasing the fertility of matings between two sickling parents. There is another rather similar factor in Africa which may act in the same way. In most, though not all African tribes, sexual intercourse between a husband and wife is prohibited while the wife has an unweaned child. Since children frequently remain at the breast for two or even three years, this provides a form of family planning in peoples ignorant of more sophisticated methods. If a child dies young, however, the prohibition lapses and the husband hastens to resume his conjugal rights. Hence deaths in infancy are partly compensated for by

a shorter interval between pregnancies. This and the psychological mechanism already mentioned would apply in sickling only to matings between two sickling parents, and it is unlikely that their general effect on the fertility of heterozygotes is very great.

2. Increased resistance to disease in heterozygous

sicklers From a study of Tables 15 and 16 it is quite clear, as we have seen, that in my population trait-bearers have no increased liability to disease as compared with normal subjects. Observing that with every main group of disorders the sickling group, despite a greater aggregate length of service, spent less time in hospital than did the normal controls, one might go a little further than this. The results suggest--though they certainly do not show conclusively--that bearers of the trait may be less liable to disease than are non-sicklers.

This is a somewhat alarming suggestion. The possibility had been briefly mentioned by Raper (1949b) who however thought it very unlikely. Neel (1951a) observed that positive selection in favour of the heterozygote would be the most logical alternative to a high mutation rate. He felt, however, that the available evidence was rather against it. We have seen that the evidence quoted by Neel and based on

studies of the incidence of sickling at various ages is not completely representative; as Table 13 shows, numerous authors have found no decrease in sickling incidence with advancing age, and one has found an increase. Other indirect evidence, based on the incidence of sickling in populations selected for health or morbidity, shows the same lack of unanimity. As Neel himself (1951a) has observed, if such an advantage in health does occur, hospital populations would still be expected to show a decreasing incidence in the higher age groups; and as many of the surveys are partly at least based on hospital populations this may well obscure the results. It is quite clear that the indirect statistical evidence based on studies of age incidence and incidence in selected populations is too contradictory to give any decisive lead.

It is somewhat surprising that, with the exception of some work by Humphreys (1952) which does not quote any figures, and my own investigation (1952b, described in this thesis) no one known to me has tried to determine directly whether sicklers are more or less liable to disease than are normal subjects. Humphreys concluded that the trait-bearers he investigated were not unduly liable to disease. My own results, while confirming this, suggest that an advantage in health may be conferred by the possession

of the trait. Further work is needed to confirm or refute this. My own views might be summarised as follows:

(a) The sickle-cell trait does not predispose to morbidity.

(b) The gene frequency is almost certainly not maintained by mutation, and it is very unlikely that it is wholly maintained by an increased fertility in heterozygotes.

(c) It is therefore very probable on biological grounds that the heterozygote enjoys some advantage as compared with normal subjects, to counterbalance the undoubted selective disadvantage under which the homozygous sickler labours. There is some slight evidence for this view in my results.

(a) and (b) have already been discussed. (c) is an article of faith, but I should be surprised if it were found not to be so. Very little work indeed has been done on the population genetics of sickling in Africa, and the question of how the gene frequency is maintained has had little attention. When confronted with the relatively enormous frequencies of the sickling gene in some parts of Africa, explanations in terms of mutation and increased fertility break down. It would be an unimaginative worker who

refrained from trying to explain the otherwise unexplainable because all the facts were not available. As Holmes was fond of observing to Watson, when all other explanations of a phenomenon have been excluded, the one that remains, however improbable it may seem, must be the right one. The discussion of this question that follows is quite frankly speculative.

When the question of sickling is considered from the viewpoint of its effects in human evolution, it is at once clear that if the gene is not being replaced by mutation its effects cannot be wholly deleterious, or it would not survive. Mutation in man is a rare event, and the only conditions that are wholly maintained by mutation are rare ones such as haemophilia. Variants occurring at higher frequency are maintained by a process of balanced polymorphism (Race and Sanger, 1950). Briefly, this works through a selective advantage conferred by the gene concerned, which at a certain level of frequency is nullified by a selective disadvantage which may be genetically or otherwise produced. In sickling the process might be as follows. The gene in its heterozygous state confers an advantage in health or fertility, or both, on its possessors, who thus increase. This increase

leads to an increase in the number of homozygous sicklers, who die before they can reproduce. Their numbers vary with the square of the gene frequency, whereas the numbers of heterozygotes are more or less directly related to it. With increasing gene frequency the rate of increase of homozygotes is thus much higher than that of heterozygotes. At a certain level of sickling frequency the loss by death of homozygotes just balances the advantage enjoyed by heterozygous sicklers, and the population comes into equilibrium at this level. As we have seen, the advantage is very unlikely to be wholly one of fertility. It is therefore very probable that a real advantage in resistance to disease is enjoyed by the heterozygous sickler. If this occurs, it is plainly very likely that the healthier sicklers will possess a slightly higher degree of fertility than normal people; the two advantages may thus very well coexist.

As we shall see later, however, the mere assumption of an advantage enjoyed by the heterozygote will not by any means completely solve the problem, though I believe that it gives the key to its elucidation. This will be dealt with later. Assuming for the moment that such an advantage exists, what

could its nature be?

Two kinds of advantage are possible: (a) the advantage might be a direct consequence of the possession of the sickling gene; (b) as Neel (1951a) has suggested, the gene might be linked to some other character of adaptive significance. These will be considered in turn.

(a) Possibility of a direct advantage due to the sickling gene. An advantage of this kind might be due to several causes, among them: (i) directly to the sickling tendency of the red cells; (ii) to some other physical characteristic of the red cells; (iii) to the structure of the spleen; (iv) to the abnormal haemoglobin in sicklers. These will be considered in turn.

(i) We have seen that in heterozygotes it is unlikely that the red cells do sickle to any significant extent in vivo; and when this occurs, as it does in homozygous sicklers, its effects are deleterious. It is thus unlikely that the sickling of the cells is the mechanism by which the advantage is produced, though it might be argued that intracellular parasites would not survive the in vivo sickling of their containing cells.

(ii). It is known that the red cells in sicklers have an increased resistance to hypotonic saline solutions. Neel (1951b) has further shown that in the sickle-cell trait the mean corpuscular volume is rather less than normal. Neither of these findings has any known adaptive significance.

(iii) Rich (1923) has shown that in sicklers the spleen is histologically abnormal. The abnormality consists in a malformation of the sinuses by which the Malpighian bodies appear to be surrounded by lakes of blood. This is apparently a direct effect of the gene as it does not appear to occur independently of the trait; it is difficult to see what adaptive significance it could have.

(iv) We have seen that in trait-bearers on the average two-fifths of the total haemoglobin is of the abnormal variety. I have suggested (1952a) that this abnormal haemoglobin might conceivably provide a less favourable environment for malaria parasites than does normal haemoglobin. This view was based on the findings in Table 17, which show that in the population examined by me the spleen is palpable in a significantly lower proportion of sicklers than non-sicklers. This was also observed by

Beet (1947). The population examined by me was drawn mostly from areas where malaria is endemic, and palpable spleens are therefore very common. It was suggested that the lower spleen rate in sicklers might be a consequence of an increased resistance to malaria, the sicklers having suffered from fewer or less severe attacks than the non-sicklers; and that this increased resistance, if it occurred, might be due to the intracellular environment in sicklers with its abnormal haemoglobin being unfavourable to plasmodia. This is conjecture, but the question needs further investigation. There are at least two other explanations of the lower spleen rate in sicklers that could be offered. One is that the histological abnormality reported by Rich (1928) is associated with a smaller spleen than normal, or with one less liable to enlargement in tropical diseases. There is no information available on this point. The other explanation, suggested by Beet (1947) is that the spleen in sicklers has become small and fibrotic as a result of repeated infarctions. This is known to happen in sickle-cell anaemia. I do not think that trait-bearers suffer ill effects of this kind. Beet regarded trait-bearers as liable to pathological effects

of sickling, and his explanation of the lower spleen rate is in keeping with this opinion. I think it more probable that trait-bearers are less liable to tropical diseases than normal persons, and that the spleen is in consequence less often found to be enlarged. The question is an interesting one because the lower spleen rate in sicklers is the only physical finding known to be associated with the trait.

(b). Advantage due to linkage between the sickle-cell trait and some character of adaptive significance. Neel (1951a) has pointed out that positive selection for the heterozygote might be due to genetic linkage between the sickling gene and some other gene or genes of adaptive significance. He quotes references to animal genetics in which linkage between haematological traits and other physical characters has been demonstrated. In man very little is known about linkage. Snyder et al. (1947, 1949) produced evidence for linkage between the sickling gene and the MN blood groups, but this was not confirmed by the later work of Neel et al. (1952). The existence of this linkage is thus doubtful, but the question is a most interesting one because there is some evidence--again unconfirmed--that the MN heterozygote enjoys a selective advantage over the MM and

NN homozygotes. Race and Sanger (1950) observe that almost all investigators have observed an excess over the expected proportion of 50% in the proportion of MN children born of MN x MN matings, and they suggest that this may be evidence of selection favouring the heterozygous form MN. The subject is discussed by Haldane (1948) who thinks that a selective advantage, probably in prenatal survival, is possessed by individuals of group MN. Further work by Wiener (Race, personal communication) does not confirm the supposed excess of MN children, however.

One might think that, once the existence of positive selection for the heterozygous sickler were established, the problem of the population genetics of sickling would be solved. Unfortunately the matter is not so simple. If the incidence of the sickle-cell anomaly were everywhere the same, one would be able to postulate a selective advantage enjoyed by heterozygotes that just balanced the loss by death of homozygous sicklers. The incidence of sickling in Africa, however, shows every gradation of incidence between 0.6% in the Karanga and 45% in the Baamba. There is little doubt that in some of the tribes the incidence of sickling is in the process of

changing, it is quite clear that they are not all tending towards the same point of equilibrium, or a more even distribution of sickling would long ago have been set up. If the proportion of homozygous sicklers in a population varied directly with the incidence of the trait, equilibrium might perhaps be maintained at any level. The incidence of the homozygote, however, varies with the square of the gene frequency. Table 19 shows the incidence of sickling in a few African tribes, together with the theoretically expected incidence of homozygous sicklers calculated from the squares of the gene frequencies.

T A B L E 20

Expected Incidence of Homozygous Sicklers
in some Bantu Tribes

Tribe	Approximate incidence of sickling, %	Expected incidence of homozygotes, % of births
Karanga	0.6	0.003
Ndau	3.5	0.03
Chewa (Nyasaland)	10	0.25
Nyakyusa	18.5	1.06
Bemba-Bisa	27	2.66
Makonde (Foy et al., 1952)	40	7.73

This shows that where the incidence of sickling is

0.6%, as in the Karanga, the homozygote/heterozygote ratio is about 1/200; whereas in the Makonde with an incidence of 40% the ratio is about 1/5. Since with changing gene frequency the homozygote/heterozygote ratio does not remain constant, one would suppose that equilibrium could be maintained at only one level of sickling incidence, if the respective adaptive values of homozygosity and heterozygosity remained constant. In fact, we find equilibrium apparently maintained at the most diverse levels of gene frequency. There are two possible explanations for this; (a) that the liability of the homozygous sickler to elimination varies from one tribe to another, and (b) that the advantage enjoyed by trait-bearers varies in the same way. The influence of selection on both homozygote and heterozygote could be modified by either genetic or environmental factors.

The existence of some modifying factors, presumably genetic, has already been observed (Neel et al., 1951). These authors have shown that there are significant intra-family correlations in the proportion of abnormal haemoglobin possessed by sickling individuals, and it appears that the amount of abnormal haemoglobin possessed by both homozygotes and heterozygotes is genetically controlled. Homozygous

sicklers might thus be less liable to pathological effects if they inherited a low proportion of abnormal haemoglobin. Other genes might also conceivably increase or mitigate the effects of the sickling gene in its homozygous state. If such genes exist, and are found to show significant differences in their incidence from one tribe to another, they would have some effect on the genetic balance between homozygous sicklers, trait-bearers, and normal individuals. There is no information on this point; but there is a certain amount of evidence to support the view that the effects of homozygosity differ from place to place in Africa. We have already seen that experienced workers in different parts of Africa, all on the lookout for sickle-cell anaemia, hold very different opinions on its prevalence. It is very probable indeed that real differences in the incidence of sickle-cell anaemia in homozygous sicklers exist in Africa. This view was expressed by an annotator in the British Medical Journal (1952, ii, 433) and it seems very likely that it is true. But little is known about the effects of homozygosity for the sickling gene in Africa.

The question of factors modifying the positive advantage enjoyed by heterozygotes is a more difficult

one, since such an advantage is not even certainly known to exist. It might well be modified in the same way by genetic factors. That the modifying factors are probably largely genetic rather than environmental is shown by the existence side by side and intermingled of tribes with very different incidences of sickling, living in very similar environments. Environmental factors might play some part, however. If, for example, it is true that sickle-cell haemoglobin provides a less favourable environment than normal haemoglobin for malaria parasites, geographical variations in the incidence of malaria would affect the genetic balance.

In our present state of ignorance further discussion of the nature of these presumed modifying factors is of little value. It is clear, however, that if as I think the balance of positive and negative selection is the mechanism that maintains the gene frequency, such factors must exist. It is at present impossible to decide whether my view is the true one or not. I think it safe to say that it is the least unlikely explanation that has been put forward, and that such a mechanism is not without biological precedent. There for the present we must leave it.

CHAPTER VIII

SUGGESTIONS FOR FURTHER WORK

The investigation described in this thesis suggests several lines along which further work might be planned.

The first and most obvious need is for further investigation of geographical and tribal incidence in Africa. Parts in which little or no published work has been done are South-West Africa, Bechuana-land, the northern part of Southern Rhodesia, a large part of Northern Rhodesia, Somaliland and Abyssinia. In other territories, with the exception of Uganda, the available information is incomplete. Throughout Africa the old tribal organisation is breaking down and valuable material is being lost. Though it is not immediately relevant to the subject, one might add here a plea for further work on the blood groups in Africa. If my view of the origin of sickling in Africa is correct, its incidence has little ethnological significance except in the elucidation of relatively recent movements. The blood groups can provide anthropological information of far greater value.

At the same time other inherited abnormalities of the blood might be sought in black Africa.

Thalassaemia is one of these. Another inherited haematological abnormality that might have anthropological significance is the Pelger-Huet abnormality of the leucocytes (Schilling, 1952). As far as I know, this rare abnormality has not been sought in Africa.

The second part of the work suggests several problems. It is not yet known whether African sicklers possess a higher or lower proportion of abnormal haemoglobin than Americans do. Electrophoretic studies of African haemoglobins are thus urgently needed. The difficulty is that where electrophoretic apparatus is available sicklers are few, and vice versa. I am at present attempting electrophoresis of haemoglobins on filter paper and hope to develop a quantitative technique. The apparent differences in the effects of sickling between America and parts of Africa may be due to differences in the proportion of abnormal haemoglobin. There may also be differences of this kind, genetically determined, between various groups in Africa; as we have seen, sickle-cell anaemia appears to be far more common in some African groups with high sickling incidence than

in others. The demonstration of significant intra-tribal correlations in the proportions of abnormal haemoglobin possessed by trait-bearers would be of the utmost interest.

A study of African homozygous sicklers would also be most informative. In an area where the incidence of the trait is high it should be possible, by genetic means and from the appearance of the sickled cells, to collect a large number of homozygotes, at any rate in children. It is not known what becomes of these in Africa; do they all die young, or do homozygotes reproduce? and what is the state of health of any that survive? Electrophoretic studies should be carried out on these homozygous sicklers to determine the proportion of abnormal haemoglobin which they possess. The question of what happens to homozygous sicklers in Africa is one of the greatest importance, both from the clinical and the theoretical point of view.

The suggestion that the trait confers a positive advantage in health needs confirmation or otherwise in a population of higher sickling incidence than mine. Such a closed community served by a single hospital should be available in Central Africa in an industrial concern, prison or military unit.

Further studies are needed of the doubtful question whether in vivo sickling ever occurs in trait-bearers as distinct from homozygotes. If it does, it must be very rare; but it might be possible to demonstrate it in trait-bearers suffering from marked anoxaemia, for example in cyanosed patients.

Methods for the culture of malaria parasites are not very satisfactory, but it would be interesting to attempt the culture of plasmodia in sickle-cell blood which was kept oxygenated to prevent the mechanical damage to the parasites which might result from sickling. Cultures in normal blood should be used as controls. This might show whether the suggestion that sickle-cell haemoglobin is an unfavourable medium for malaria parasites has any truth in it.

In an area of high sickling incidence, histological confirmation of Rich's (1928) spleen findings is needed. As far as I know this has not been attempted in Africa, and it is not certain whether the abnormality observed is simply a dilatation of the sinuses surrounding the Malpighian bodies or whether there is a radical difference in the structure of the spleen in sicklers.

CHAPTER IX

SUMMARY

The work deals with the sickle-cell trait, not with sickle-cell anaemia. It is based on the examination of 3081 adult male Bantu mine workers, in whom sickle-cell anaemia has not been observed. The problems dealt with are:

1. The distribution of sickling in Africa, and its anthropological significance.
2. The question of the clinical effects of the sickle-cell trait.
3. The population genetics of sickling, with special reference to the question of why a gene with deleterious effects in the homozygous state is not eliminated by selection.

CHAPTER I. A general introduction deals briefly with the history of the trait, methods by which it may be demonstrated, the distinction between the sickle-cell trait and sickle-cell anaemia, and the mechanism of sickling. The genetics of sickling is reviewed and the view of Neel and Beet--that sickle-cell anaemia is for practical purposes a disease of individuals homozygous for the sickling gene--is accepted as a working hypothesis. The work thus deals with the heterozygous sickler or bearer of the sickle-cell trait.

CHAPTER II. Distribution of Sickling in Africa:
Introduction.

(a) The findings of workers who have investigated the incidence of sickling in various parts of Africa are arranged in a series of tables.

(b) The anthropological explanations offered by some of these authors are reviewed.

(c) The discovery by Lehmann and Cutbush of the sickle-cell trait in Veddids of South India is noted. These authors found an incidence of sickling of 31% in Indian Veddids, but no increased incidence of the typically African Rh chromosome cDe. They therefore postulated a migration from the east through Southern Arabia bringing the sickle-cell gene to Africa after the Negro races had established themselves.

CHAPTER III. Distribution of Sickling in Africa: Original Work.

(a) Adult mine labourers of various tribes were examined at Shabani and Mashaba, Southern Rhodesia. This population contains very few closely related persons, and evidence is adduced to suggest that all the sicklers in it are true trait-bearers (heterozygous sicklers) and not individuals liable to sickle-cell anaemia. Subjects are mostly young adults and were on engagement for work relatively fit men. This population is a highly selected group. My own findings are compared with those of authors who have examined the same tribes in their home surroundings, and it is found that the selection that has taken place in making up the population has not discriminated against bearers of the trait.

(b) The techniques used to elicit sickling were (i) the Beck and Hertz tube method for the first 1000 bloods and subsequently (ii) the sodium metabisulphite method of Daland and Castle.

(c) Results. 3081 examinations showed an overall percentage of 4.8% sickling. Findings were classified geographically, and by tribe with geographical subdivisions. The highest overall geographical incidence observed was 16.7% in Northern Rhodesia and the lowest 0.6% in Southern Rhodesia. The highest tribal incidence found was 27% in the Bemba-Bisa of Northern Rhodesia, and the lowest 0.63% in the Karanga of Southern Rhodesia. Five Central African territories and thirteen tribes were represented. The observed differences were analysed statistically.

CHAPTER IV. Distribution of Sickling in Africa: Discussion.

(a) All available results, including my own, have been used to prepare a map showing the general trends of sickling incidence in Africa. This map shows a moderate incidence in the true Negroes of West Africa. In a large block of Central African Bantu tribes there is a moderate to high incidence, with a general trend towards higher incidence in the east. South of the Zambesi River the trait appears to be rare.

(b) The area covered by my own survey is considered in more detail with a map on a larger scale. The Karanga of Southern Rhodesia, who resemble the Bantu north of the Zambesi in language and totemism, are shown to have the low incidence of sickling (0.6%) characteristic of the tribes of the Union of South Africa, whom they resemble in being patrilineal in their system of succession.

(c) A gradient of increasing sickling incidence from east to west in the region of the southern end of Lake Nyasa is described, and is explained by the existence of a block of high-incidence tribes, the Bemba-Bisa-Lala-Lenje, in north-western and western Northern Rhodesia, towards which the incidence of sickling approximates as one travels westwards. This gradient is demonstrated in the two known offshoots of the Nyanja tribe, the Chewa and Senga. Using the technique of Elsdon-Dew, based on gene frequencies, the approximate percentage composition of the Chewa and Senga tribes in terms of Nyanja and Bemba-Bisa-Lala mixtures is calculated. Linguistic differences have been described which parallel the variations in sickling incidence from east to west. It is predicted that the incidence of sickling in the Lenje tribe of Northern Rhodesia should be found to be higher than that in the Senga (20%). The boundary of the Central African block of high-incidence tribes is defined for some distance in the region of Lake Nyasa by means of the isogene $p = 0.1$.

(d) The origin of the sickle-cell trait in Africa is discussed and it is shown that the view of Lehmann and Cutbush, that the gene was introduced comparatively recently from the East after the establishment of the black races, will account well for the observed facts in the Bantu. It would have to be postulated that the trait did not extend south of the Zambesi River.

(e) A theory that will explain the observed facts in Africa must account not only for the possession of the gene by the Bantu--as this theory will--but for its existence in the non-Bantu negroes of West Africa even though it was introduced into the Bantu after the negro-Bantu differentiation had taken place.

(f) This difficulty is resolved by the existence of a human migration from the east which took place comparatively recently and was accompanied by the Shorthorn Zebu variety of Indian cattle, by the present distribution of which in Africa the paths of the migration may be traced. This migration, consisting of Indians and Arabians, entered Africa from Southern Arabia, probably after 700 A.D. One branch spread southwards down the east coast as far as the Zambesi River, which it did not cross, and thence to Madagascar. The second branch extended

across the continent to the Gulf of Guinea, where shorthorn zebus are to be found today, and the strain has had considerable influence on the cattle of the West African negroes. It is suggested that the sickling gene was brought to Africa by the human migration which brought the shorthorn zebu. Its direction will explain the low incidence of sickling in Africa south of the Zambesi, which the migration did not cross; the generally higher incidence in the Bantu near the east coast, where the gene was introduced; and the presence of the gene in the West African negroes. The low incidence of sickling south of the Zambesi is then not a sign of ethnological unity in the Southern Bantu but means simply that the comparatively recent migration of the sickling gene did not extend south of the river. It is predicted that if this theory is true the population of Madagascar should show a higher incidence of sickling than do the tribes on the mainland south of the Zambesi, since the shorthorn zebu occurs in Madagascar.

CHAPTER V. Effects and Population Genetics of the Sickle-Cell Trait. Introduction.

1. Effects of the Sickle-Cell Trait.

(a) Indirect evidence, derived from a study of the incidence of the trait in populations selected for physical fitness and in unfit populations, is reviewed. The evidence thus obtained for or against the trait as a cause of morbidity is conflicting.

(b) Investigations of the incidence of sickling in various age groups are reviewed. There is no agreement in the results.

(c) Direct evidence from a study of trait-bearers and their diseases is reviewed. Several authors have expressed the opinion that the trait predisposes to morbidity. Others have regarded it as of no clinical significance. The principal specific effects for which the trait has been blamed are reviewed. Most of them are a consequence of sickling in small vessels with consequent interruption of the blood supply. Effects of intravascular sickling which have been observed in sicklers exposed to low oxygen tensions while flying or experimentally are described.

2. Population Genetics of Sickling.

(a) Those who develop sickle-cell anaemia seldom survive to reproductive age, and if they do have a

greatly reduced fertility. With the loss of some sickling genes in this way in each generation one would expect that the incidence of sickling would decline and that the gene would finally disappear.

(b) In Africa it is not certain what proportion of homozygous sicklers develop sickle-cell anaemia, and it seems probable that this proportion varies from one part of Africa to another. Some homozygotes at any rate develop the disease in all parts of Africa where sickling occurs.

(c) Of the mechanisms which might act in keeping up the gene frequency, mutation has been suggested by one author. However this seems improbable because of the incredibly high mutation rate which would have to be postulated in a tribe of high sickling incidence, and because the rate would have to be different in almost every tribe.

(d) Neel has observed that positive selection in favour of the trait-bearer--i.e. an advantage in health or fertility over the normal--would be the most probable alternative to mutation, but in his opinion (1951) the then available evidence was rather against it.

(e) Foy and Kondi have suggested that the gene frequency is maintained by an increased fertility in trait-bearers, combined with selective mating between sicklers.

CHAPTER VI. Effects of the Trait and Population Genetics. Original Work.

(a) It is shown that in my population there are no significant differences between the rates of sickling in fit men and those admitted to hospital. The lowest incidence in fact is found in 193 patients admitted to medical wards.

(b) The hospital records, some going back 25 years, of a group of 50 sicklers are compared with those of 50 non-sicklers of similar tribe and length of service. With every main group of disorders the sickling group spent less time in hospital than did the non-sicklers.

(c) Sicklers are shown to have a significantly lower incidence of palpable spleens than non-sicklers.

(d) The sickle-cell trait is without effect on body weight in the population examined by me.

(d) Adult sicklers and non-sicklers were questioned on the sizes of the families (live births) from

which they were derived. There is no significant difference between the sizes of the families in the two groups, but this part of the investigation is inadequate.

Chapter VII. Effects and Population Genetics of the Trait. Discussion.

1. Effects of the Trait.

(a) It is clearly shown that in the population examined by me the sickle-cell trait does not predispose to morbidity. The findings suggest further that trait-bearers may enjoy a slight advantage in health over normal subjects.

(b) Some workers have held that the trait does predispose to disease. It is suggested that in the populations examined by these workers trait-bearers may have been mixed with a proportion of homozygous sicklers. These homozygotes are liable to sickle-cell anaemia and are almost certainly also unduly liable to disease of other kinds. The finding of other workers that the incidence of sickling is higher in young subjects than in older ones may be explained in the same way, by the presence in the younger groups of homozygotes who are selectively eliminated as time goes on.

(c) The specific vascular complications of sickling are probably confined to homozygotes and do not, for practical purposes, occur in bearers of the trait.

(d) A case is described in which extensive sickling found at autopsy seven hours after death was thought to be the cause of death until a blood smear taken just before death was examined and found to show no sickled cells. It is suggested that post-mortem sickling may be rapid and may confuse the picture in these cases.

(e) As these results suggest that the sickle-cell trait is unassociated with any pathological manifestations, it is suggested that the terminology of sickling should be changed if the results are confirmed. The term "sickle-cell disease" should be retained, since anaemia is not the only pathological manifestation of sickling; but it should not be applied to the sickle-cell trait. The classification suggested is:

1. Sickle-Cell Disease, including sickle-cell anaemia and primarily vascular manifestations.

2. Sickle-Cell Trait, a state which is pathological only genetically.

2. Population Genetics of Sickling.

(a) The mechanisms that could act in keeping up the gene frequency, if mutation is eliminated, are as follows:

(i) Increased fertility in trait-bearers, combined, in the opinion of Foy and Kondi, with selective mating.

(ii) An advantage in health enjoyed by trait-bearers over normal subjects.

(b) Increased fertility in heterozygotes is considered. There is no evidence for or against this except for my own investigation, which is inadequate. A psychological mechanism, by which deaths during infancy are over-compensated, may have some slight effect in sickling. It is shown that in a tribe of high sickling incidence the increase of fertility in trait-bearers would have to be very great to compensate for the loss of homozygotes. It is thus unlikely that the sole mechanism at work is one of increased fertility. Selective mating between trait-bearers is unlikely to occur since there is no way short of examining the blood of identifying a heterozygous sickler.

(c) My own results suggest that trait-bearers may be more resistant to disease than are normal subjects. Since the gene frequency is not maintained by mutation and it is very unlikely that it is maintained by increased fertility in heterozygotes, it is very probable that this advantage in health in trait-bearers suggested by the results is a real factor in keeping up the gene frequency. It is suggested that in sickling we have an example of a balanced polymorphism, the negative selection against homozygous sicklers being balanced by positive selection for bearers of the trait.

(d) Assuming the existence of an advantage in health enjoyed by trait-bearers, its possible nature is considered. In view of the finding that the spleen is palpable in a lower proportion of sicklers than non-sicklers, it is suggested that trait-bearers may be abnormally resistant to malaria, perhaps by virtue of their abnormal haemoglobin offering an unfavourable environment for the parasites.

(e) The suggestion of Neel that the sickling gene might be linked with some other character of adaptive significance is considered. The linkage of the gene with the MN blood group system has been

reported. Some evidence is mentioned suggesting that the MN heterozygote enjoys a selective advantage over MM and NN homozygotes, but this has not been confirmed.

(f) The mere assumption of an advantage in health enjoyed by heterozygous sicklers will not fully account for the equilibrium which is apparently maintained between homozygotes and heterozygotes at the most diverse levels of gene frequency. It is suggested that this equilibrium must be affected by a number of modifying factors, probably both genetic and environmental.

Chapter VIII. Suggestions for Further Work.

In this chapter some lines of further research are suggested.

APPENDIX

NOTES ON TRIBES EXAMINED IN ORIGINAL WORK

The tribal groups into which subjects have been classified in Chapter III need some explanation and definition. Every native, except the completely urbanised, knows to which tribe he belongs; but not all of these tribal groups are of pure stock. Some, such as the Karanga, have probably preserved their identity more or less intact for hundreds of years; others, for example the Cikunda and Sena, are agglomerations with only a habitat in common. The accurate classification of natives by tribe is by no means as simple as it would appear; many of the tribes have several synonyms and subdivisions, and careful questioning is essential. The greatest care has been taken to make the classification as reliable as possible.

ANGONI The nucleus of the Angoni was one of the groups of South African Bantu from Natal who fled from the tyrant Chaka in about 1820. The Angoni, led by Zwangendaba, travelled northwards to what is now Southern Rhodesia; after a brief stay here, where they subjugated the ruling vaRozwi clan, they

went on across the Zambesi River in about 1835. It has been estimated that the contingent numbered only about a thousand at that time (Tew, 1950), although it had already absorbed elements from the Suto and Thonga tribes as well as Shona from Southern Rhodesia. After complicated movements and encounters the Angoni finally settled in six main groups. There are three of these in Nyasaland: Mombera's Angoni in the Mzimba district, extending into Northern Rhodesia at Lundazi; Ciwere's Angoni in the Dowa district; and Gomani's Angoni in the Dedza district, some of whom extend into Portuguese East Africa. There is one group (examined for sickling by Beet, 1947) in the Fort Jameson district of Northern Rhodesia; one is in Tanganyika (Lindi) and one in the Belgian Congo on the west shore of Lake Tanganyika.

It is clear that these groups of Angoni were originally small and that their biological effect would be relatively slight. The persistence of the Angoni name and culture is due to the prestige of these conquering invaders. They have intermarried with the local inhabitants and the large populations who today describe themselves as Angoni probably have little of the Zulu and Swazi in their genetic make-up. It is interesting to note that the Zulu language has

disappeared from the everyday speech of these northern Angoni, who now speak the languages of the regions in which they have settled.

The Angoni in the mining population from Northern Rhodesia are from the Fort Jameson district. The Nyasaland Angoni are almost all from the two southern groups (Gomani's and Ciwere's) with Gomani's predominating.

ANGURU This is a convenient term, meaning "foreigner", used by the inhabitants of Nyasaland to describe peoples living to the East of Lake Nyasa. It includes the Makua and Lomwe tribes occupying the north-eastern part of Portuguese East Africa, and also the Kokora and Cuabo tribes to the south of these (See Fig. 2, back end-papers). There are no Makua in the Anguru of the mining population, which consists of Lomwe, Cuabo and Kokora.

BEMBA-BISA These two tribes occupy the north-eastern part of Northern Rhodesia. Both are mentioned by Lacerda, who visited the region in 1798 (Doke, 1931).

CIKUNDA-SENA These are mixed peoples living along the Zambesi River, where they have for centuries been influenced by the Portuguese settlements on the river.

The Cikunda, several hundred miles upstream, are related to the Senga of the Petauke district (Tew, 1950); the name is derived from a verb meaning "to conquer" and was applied to those employed by the Portuguese as soldiers and messengers. The Sena, further downstream, apparently take their title from the district of that name.

KARANGA The Karanga are a branch of the Shona of Southern Rhodesia, and occupy the southern part of the colony. They are the most numerous tribe in the mining population. Early Portuguese records mention the Karanga under their king Monomotapa. In 1561 Father da Silveira was martyred by the Karanga in what is now Mashonaland, an event that was followed by a miracle. The Karanga together with the other Shona tribes are interesting in that they form a group intermediate between the southern Bantu tribes of the Union of South Africa and the tribes north of the Zambesi. The tribes of the Union are patrilineal and patrilocal; that is, inheritance descends through the male and a wife on marriage goes to live in the village of her husband. The Shona of Southern Rhodesia are also patrilineal and patrilocal, but in language and their highly

developed system of totemism they are closer to tribes north of the Zambesi which are matrilineal and matrilocal. Briefly, totemism in the Karanga consists in each individual belonging to a clan distinguished by a totem (mutupo, plural mitupo), which is usually though not always the name of an animal or a part of the body (e.g. Shumba, lion; Zhou, elephant; Gumbo, leg; Moyo, heart). There are certain magical prohibitions or taboos regarding the totem object; for example, members of the Lion clan must avoid the flesh of lions. Each clan may be further subdivided and the system provides the prohibited degrees within which marriages may not be contracted. Bullock (1950) believes that the totem names all have ultimately a sexual significance, and that the system originated in the extreme abhorrence of incestuous unions which seems to be common to all savage tribes and has given rise to the mother-in-law joke.

NDAU The Ndau are also of Shona stock; they occupy the part of Portuguese East Africa from the eastern border of Southern Rhodesia, where they meet the Karanga, to the coast. In appearance and language they are slightly different from the Karanga, though the dialects are mutually understood. Their

territory adjoins that of the Shangaans to the south and they have been influenced by the Zulu invasion under Gungunyana (see Shangaan). They will frequently describe themselves as Shangaans but in this work the tribes have been carefully distinguished on the basis of language, the Ndaou language being totally different from that of the southern tribes. The coastal Ndaou at Sofala were visited by dos Santos (Junod, 1938) who recorded some words of their language. Arab writers of the tenth century described the people as being of hideous figure and deformed complexion, speaking with "a species of hissing."

NYAKYUSA The Nyakyusa are a branch of the Ankonde of northern Nyasaland and southern Tanganyika. They file their upper incisors to points and are said to subsist chiefly on milk and bananas. Unlike most of the northern tribes they have a patrilineal system of succession. All the Nyakyusa investigated are from the Tukuyu district of southern Tanganyika.

NYANJA-CHEWA-SENGA The Nyanja (meaning lake-dwellers) inhabit the eastern and southern shores of Lake Nyasa. They are closely related to the adjacent Yao, and have a tradition of having come from the Luba district of

the Congo at some time before 1500 A.D. The history of the Chewa and Senga is known. The Chewa seceded from the Nyanja during the eighteenth century, and travelled westwards towards Northern Rhodesia where there is a large population in the Fort Jameson district. The Senga of Petauke (not to be confused with a more northern group of the same name who regard themselves as the only true Senga, a view that prevails also in the southern group) split off from the Chewa between 1800 and 1860 and spread still further west towards the Lala and Lenje tribes, with whom they intermarried. As would be expected, the Senga language holds an intermediate place between the Nyanja group on one hand and the Bemba-Bisa-Lala on the other; there is a tendency for the sibilants to soften from east to west in the area in which Senga is spoken (Tew, 1950).

SHANGAAN This is a convenient term in very general use by Thonga-speaking peoples of southern Portuguese East Africa and the southern part of Southern Rhodesia. The true AmaTshangana were an offshoot of the Natal Zulus who penetrated into these regions under their chief Gungunyana; as with the Angoni, their numbers were probably not large. The Shangaans in the mining

population are all from the Hlengwe clan of Portuguese East Africa and the adjacent south-eastern corner of Southern Rhodesia.

YAO The Yao occupy Nyasaland and a large tract of Portuguese East Africa to the East of the Nyanja. In culture and language they resemble the Nyanja, but are more warlike and were only subdued by the British with difficulty. They have had long contact with the trading Arabs of the coast and most of them are Mahommedans.

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